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ARTIFICIAL RESPIRATION BY MOUTH-TO-MASK METHOD*

A Study of the Respiratory Gas Exchange of Paralyzed Patients Ventilated by Operator's Expired Air

JAMES O. ELAM, M.D.,† ELWYN S. BROWN, M.D.,‡ AND JOHN D. ELDER, JR.§

BUFFALO, NEW YORK, AND ST. LOUIS, MISSOURI

VENTILATION and the respiratory blood gases have recently been measured in apneic adults to determine the relative merits of the manual methods of artificial ventilation.[1-9] Comparable data have not been reported concerning the simple and apparently effective procedure of mouth-to-mouth insufflation, one of the oldest known means of resuscitation.[10-13] Numerous writers have endorsed the mouth-to-mouth method,[12-22] which obstetricians have long practiced in infants with asphyxia neonatorum. Anesthetists occasionally inflate the apneic patient's lungs with expired air after endotracheal intubation. The five-year survey of Ross[23] indicates that the ancient method is infrequently used by rescue personnel. Whittenberger and Sarnoff[13] attribute this neglect to the bystander's reluctance to come into direct contact with the lips of the moribund person. Interposing a mask between patient and operator overcomes this objection. Insertion of a disposable cotton filter would prevent cross-contamination. This mouth-to-mask method deserves consideration because of the inherent efficiency of expiratory inflation for transferring oxygen into the patient's lungs. The "power unit" of this form of resuscitator is as available as the person who discovers the apneic victim; oxygen is instantly restored to the lungs, and the operator is immediately aware whether his attempts are thwarted by airway obstruction. The purpose of this study is to submit mouth-to-mask artificial ventilation to an objective analysis comparable to the investigations recently carried out by others on the several manual methods.

*From the Division of Anesthesiology, Department of Surgery, Washington University School of Medicine, St. Louis.

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†Associate, University of Buffalo School of Medicine; director, Department of Anesthesiology, Roswell Park Memorial Institute.

‡Principal research scientist, Department of Anesthesiology, and associate in anesthesiology, Roswell Park Memorial Institute.

§Assistant professor of anesthesiology, Washington University School of Medicine; associate anesthesiologist, Barnes Hospital.

GENERAL CONSIDERATIONS

In 1743 a surgeon, William Tossach,[24] reported a successful application of the mouth-to-mouth method. The patient, a coal miner, was rescued after exposure in a mine that had been on fire and closed. He was pulseless and apneic, with cold skin. Tossach applied his mouth to the patient's, occluded the nostrils and inflated the lungs by his breath. A precordial beat, peripheral pulse and respirations were observed immediately. After four hours the patient walked home, and in four days he returned to work.

Fothergill thought this to be the first case in which artificial inflation of the lungs had put the heart in motion and rescued a life.[25] He strongly recommended mouth-to-mouth insufflation as a simple, inexpensive, harmless and prompt method that could be instituted by any unskilled bystander. He preferred mouth-to-mouth insufflation to the bellows because of availability and the likelihood that the patient's lungs would not be injured by the force applied.

In 1774 the Royal Humane Society was founded to promote effective artificial respiration.[26] At first the earlier Dutch methods were advocated, including warmth, mouth-to-mouth insufflation, fumigation, friction, stimulants and bleeding. According to Keith[26] all these but warmth and rubbing were discredited by the Royal Humane Society within fifty years. William Hunter referred to the practice of mouth-to-mouth insufflation to restore stillborn children. John Hunter preferred the bellows and suggested that oxygen, discovered two years before by Priestly, might prove more efficacious than air. In 1782 the Royal Humane Society recommended inflation by bellows in preference to mouth-to-mouth insufflation.[26] However, for resuscitation of the newborn, mouth-to-mouth insufflation continued to be used without the official endorsement of medical organizations.

Various mouth-to-mouth methods have been recommended by Heald,[14] MacKenzie,[15] Waters and

Bennett,[10] Tovell and Remlinger,[16] Alexander and Martin,[17] Leigh and Richardson,[18] Rossiter,[19] Flagg,[20] Graber,[21] McIntyre[22] and Whittenberger and Sarnoff.[13] The advantages claimed include efficiency of hyperventilation governs the duration of effective mouth-to-mask ventilation.

In this study, ventilation and respiratory blood gas concentrations were ascertained to test the efficiency

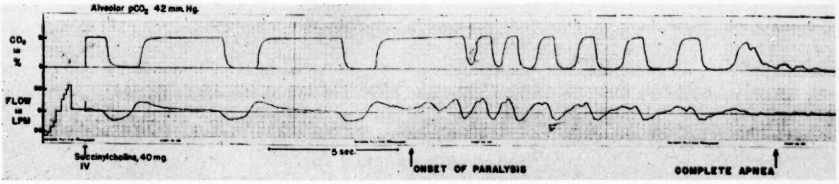

FIGURE 1. *The Effect of Intravenous Administration of Succinylcholine on Expired Carbon Dioxide Concentrations and Respiratory Flow.*

The patient breathed to and fro through the sample cell of the infra-red CO_2 analyzer and pneumotachograph screen. Twelve seconds after the injection of succinylcholine the expiratory flow pattern was altered. Respiratory muscle paralysis became complete within the ensuing thirteen seconds, and the subsequent small excursions were produced by the cardiac cycle. Mouth-to-mask ventilation was then immediately instituted.

the method,[12,14,20,22] carbon dioxide content of expired air as a respiratory stimulant,[15,19,20] capability of better ventilation than manual methods[13] and ideal temperature and volume at optimal respiratory rate.[20] Objections cited consist of reluctance of rescuers to come in contact with the lips of the subject,[13,25] low oxygen content of expired air of the operator,[14] inability of the operator to continue the method rapidly enough or long enough,[14,20] danger of gastric dilatation[20] and the possibility of lung rupture.[14,27] Prevention of cross-contamination has been suggested by use of a handkerchief[12] or a cotton filter.[17] Indirect procedures that permit transfer of the insufflation through a breathing tube and mask placed on the patient's face have been described.[15,17,21]

Although expired air is normally lower in oxygen and higher in carbon dioxide concentrations than ambient air, it is apparent that alveolar tensions are also influenced by the alveolar ventilation. From accepted normal respiratory data in man the adequacy of the mouth-to-mask method is predictable. The alveolar gas tensions of operator and patient may be calculated for various respiratory minute volumes. These estimates indicate that normal carbon dioxide and oxygen tensions (pCO_2 and pO_2) should be attainable in the patient if the operator hyperventilates while executing mouth-to-mask ventilation. The tolerance of the operator to the hypocapnia attending this of mouth-to-mask ventilation, with particular attention to hypocapnia of the operator.

METHODS AND PROCEDURE

Arterial and Ventilatory Measurements

Mouth-to-mask or mouth-to-tracheal-tube ventilation was performed on adult surgical patients in the immediate postoperative period before recovery from general anesthesia. Expired CO_2 and respiratory flow were first recorded to establish control values. The total volume of the inflation and expiration of the patient passed through the CO_2 analyzer and pneumotachograph (to-and-fro sampling).* During artificial ventilation the operator's alveolar pCO_2 was also recorded with each inflation of the patient's lungs. An intravenous drip of succinylcholine in saline solution was started, and the rate of infusion adjusted to produce cessation of respiratory flow (Fig. 1). At the onset of apnea, as indicated by the pneumotachograph record, mouth-to-mask or mouth-to-tracheal-tube ventilation was instituted. After an interval of five to thirty minutes of artificial ventilation, arterial samples were collected. Van Slyke analyses of O_2 content and capacity and CO_2 content were completed within three hours of arterial sampling; pH measurements

TABLE 1. *Arterial Blood-Gas Determinations on Patients Ventilated by the Mouth-to-Mask Method.*

EXPERIMENT NO.	O_2 SATURATION %	CO_2 CONTENT *vol. %*	pH	pCO_2* *mm. of mercury*
1	96.0	51.7	7.39	36
2	91.3		7.32	
3	93.7	45.2	7.31	37
4	100.0	41.5	7.46	24
5	94.1	42.8		
6	90.3	46.0		
7	90.1	50.1		

*Estimated.

*The pneumotachograph used was designed after that of Silverman and Mead. The Infra-red CO_2 analyzer employed was Model 16 Liston-Becker. Recording was by a Sanborn Twin-Viso.

were started within five minutes. Oximetry was employed to monitor changes in arterial O_2 saturation in initial trials of the method.[28] The breath-to-breath analyses of alveolar pCO_2 of both patient and operator during mouth-to-tracheal-tube ventilation are presented in Figure 2. Since the CO_2 analyzer remained attached to the patient's endotracheal tube, the operator's alveolar pCO_2 was recorded as he inflated the patient's lungs. Then during passive expiration the patient's alveolar pCO_2 was recorded. Reference to the simultaneous pneumotachograph and CO_2 records clarifies these events.

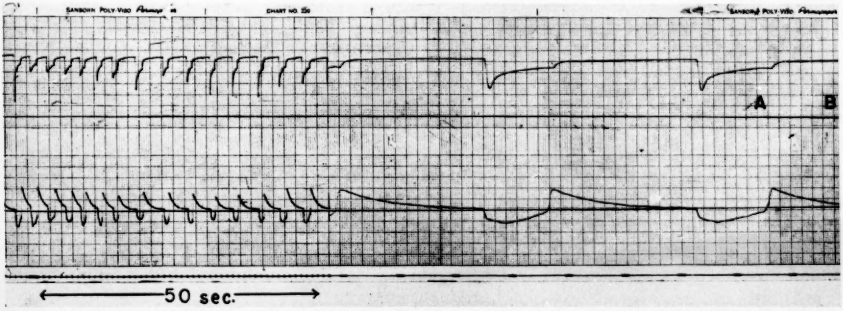

FIGURE 2. *Simultaneous Records of Respired Carbon Dioxide and Flow during Mouth-to-Tracheal-Tube Ventilation. The instruments are interposed between the operator's lips and the endotracheal tube of the patient. Recorder-paper speed is increased to show curves in detail. Inflation of the patient's lungs by expired air of operator appears in the flow record (lower tracing) as the dome-shaped curves below the zero line. The CO_2 record (upper tracing) during this interval indicates the alveolar pCO_2 of the operator* (A). *The patient's expiratory flow appears above the zero line, and during this interval his alveolar pCO_2 is recorded* (B).

Either the rate or the volume of inflations was decreased if the operator experienced dizziness.

Mouth-to-Tracheal Tube Method

Intermittent inflations were carried on as with the mouth-to-mask method except that the detectors of the CO_2 analyzer and pneumotachograph were interposed between the patient's endotracheal tube and the operator. The effective dead spaces rebreathed by the patient during the methods described above were 260 cc. for the mouth-to-mask and 195 cc. for the mouth-to-tracheal-tube procedure.

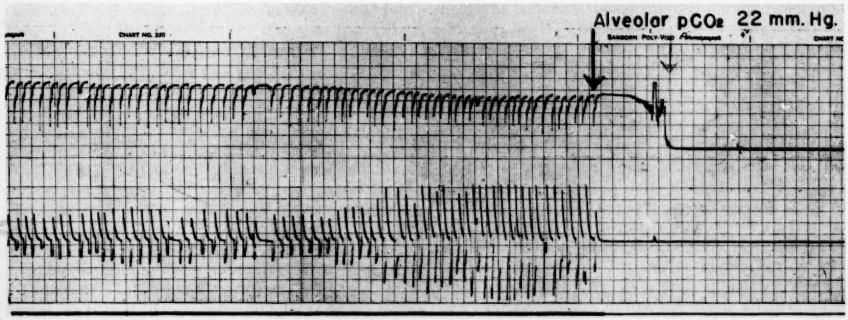

FIGURE 3. *Carbon Dioxide and Flow Record during Maximal Mouth-to-Mask Inflation.*

The larger excursions in the flow record indicate the ninety-five-second period of severe hyperventilation. This maneuver decreased the patient's alveolar pCO_2 to 22 mm. and caused dizziness in the operator, whose alveolar pCO_2 was reduced to 16 mm. of mercury.

Mouth-to-Mask Method

An anesthesia mask with 110 cc. of dead space was fitted over the patient's nose and mouth and held securely by manual bilateral support. The operator took a deep breath of ambient air, applied his lips around the ferrule of the mask and inflated the patient's airway and lungs until lift of the upper chest was observed. The operator then removed his lips from the mask, turned his head to one side and inspired ambient air while the patient exhaled through the mask.

Results

The O_2 saturation, CO_2 content, pH and calculated pCO_2 of the patient's arterial blood during mouth-to-mask ventilation are given for 7 experiments in Table 1. Mouth-to-mask ventilation consistently produced an oxygen saturation of 90 per cent or higher. In Experiment 4 the operator continued hyperventilation for five minutes and noted dizziness; the high O_2 saturation and the hypocapneic CO_2 value in this experiment are consistent with the analyses of continuous alveolar air obtained with the mouth-to-tracheal-tube method. In the other 6 experiments no dizziness was noted by any of the three operators.

The maximal hyperventilation during mouth-to-mask ventilation that would not cause dizziness in the operator was studied. Figure 2 presents a typical record obtained with the mouth-to-tracheal-tube method. To produce an alveolar pCO_2 of 32 mm. of mercury in the patient, the operator's alveolar pCO_2 was consistently reduced to a value 8 to 10 mm. below that of the patient. None of the operators noted dizziness while performing mouth-to-tracheal-tube ventilation for thirty minutes during these additional experiments.

To evaluate the effect of dizziness on the operator's performance of mouth-to-mask ventilation, one operator carried out maximal tidal inflations at a rate of 22 per minute (Fig. 3). After ninety-five seconds the patient's alveolar pCO_2 was reduced to 22 mm. of mercury, and severe dizziness was noted by the operator, whose alveolar pCO_2 was then 16 mm. After a rest of thirty-five seconds he was able to resume mouth-to-mask ventilation.

An emergency resuscitation was simulated in which respiratory failure developed over an interval of several minutes and a bystander instituted mouth-to-mask ventilation (Fig. 4). The five-minute control record before paralysis indicated a steady state with the patient maintaining an alveolar pCO_2 of 38 mm. of mercury (Fig. 4). After intravenous administration of succinylcholine the patient's respiratory muscles became progressively weakened during the next two and a half minutes. When mouth-to-tracheal-tube ventilation was started the patient's alveolar pCO_2 was 49 mm. of mercury but, with moderate volumes of tidal inflation, it was restored to the previous normal value within thirty-five seconds.

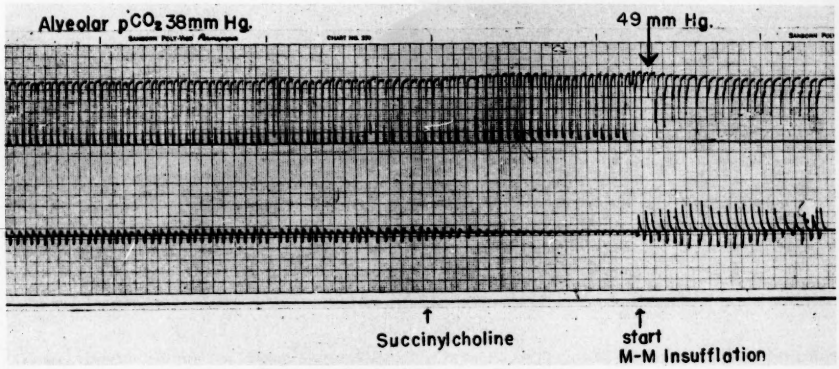

Figure 4. *Simulated Emergency Resuscitation.*

The initial five minutes of the record (before succinylcholine) was recorded to determine the patient's control values. During spontaneous breathing an alveolar pCO_2 of 38 mm. of mercury was maintained. Two minutes after the administration of succinylcholine respiratory-muscle paralysis had progressed to near-apnea. After the inflation by the operator the CO_2 record showed that the period of preceding hypoventilation had allowed the patient's alveolar pCO_2 to increase to 49 mm. of mercury. In thirty-five seconds of mouth-to-tracheal-tube ventilation the patient's alveolar pCO_2 had been restored to the previous value.

Another experiment was performed to determine whether the patient's alveolar pO_2 could be maintained within normal limits without concomitant hypocapnia in the operator (Fig. 5). Before paralysis the patient maintained an alveolar pCO_2 of 45 mm. of mercury. After the period of apnea, induced by 40 mg. of succinylcholine intravenously, the pCO_2 rose to 55 mm. of mercury. During seven minutes of mouth-to-tracheal tube ventilation, the patient's arterial O_2 saturation was maintained between 93 and 94 per cent, and the alveolar pCO_2 was gradually reduced to 49 mm. of mercury.

This interval of hyperventilation by the operator reduced his alveolar pCO_2 from 43 to 38 mm. of mercury. It was apparent that continuation of the procedure would further lower the alveolar pCO_2 of both operator and patient. During this experiment, a further modification of the method was tested. To minimize the hypocapnea of the operator his dead space was artificially increased by means of an inter-

posed tube between mask and operator. The section of the record marked modified M-M I in Figure 5 shows that the patient's alveolar pCO_2 was maintained at 45 mm. of mercury with lesser volumes of tidal inflation than those employed in the next sequence (without interposed tube).

Discussion

The present study represents the first objective evaluation of mouth-to-mouth insufflation to be reported. Normal respiratory blood-gas exchange of the patient was consistently produced by mouth-to-mask or mouth-to-tracheal-tube ventilation. These results appear to be sufficient to establish the general applicability and adequacy of the method. Moreover, the efficiency with which ventilation by expiratory inflations re-establishes normal O_2 and CO_2 exchange of the patient is striking.

Objections to mouth-to-mouth insufflation on the basis of an O_2 deficit or CO_2 excess in expired air are unwarranted since moderate hyperventilation by the operator overcomes both these theoretical limitations. It is doubtful if physical fatigue, per se, is a limiting factor for mouth-to-mask ventilation in comparison with the other manual methods.

More exact criteria are desirable by which the operator may know that the patient's gas exchange is optimal during mouth-to-mask insufflation. However, the lift of the patient's upper chest and the operator's threshold for dizziness serve as satisfactory indexes for practical purposes.

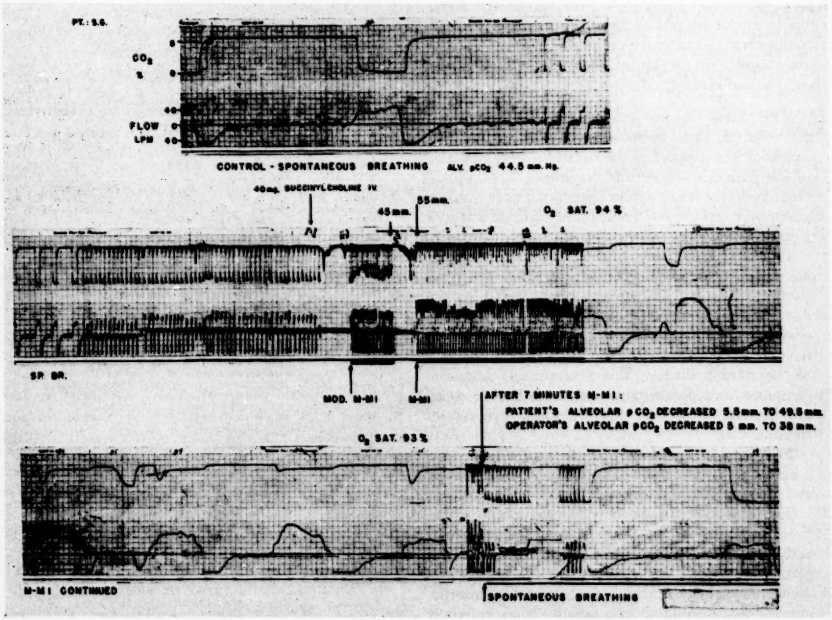

Figure 5. *Modification of the Mouth-to-Mask Method to Reduce Hypocapnia of Operator.*

After recording of the anesthetized patient's spontaneous ventilation and alveolar pCO_2 40 mg. of succinylcholine was given intravenously. The preliminary mouth-to-mask ventilation (modified M-M I) was carried out with an increased external dead space. After eighty-five seconds artificial ventilation was discontinued for fifty seconds and then continued for seven minutes without the increased external dead space (M-M I). Although the use of the added external dead space was more efficient both procedures maintained the patient's alveolar pCO_2 within an acceptable range.

The data of Otis et al.,[29] Rahn and his associates[30] and Barach and his co-workers[31] on performance as related to hypocapnia demonstrated a critical minimum alveolar pCO_2 of 25 mm. of mercury below which performance becomes progressively worse. Performance was measured in terms of hand steadiness, choice reaction time, multiplication time and contrast discrimination. These impairments are apparently not correlated with significant reduction in efficiency for performing the simpler motor functions involved in

mouth-to-mask ventilation. In a series of 23 resuscitations in which mouth-to-mask ventilation was administered by 5 operators, neither dizziness nor other symptoms of hypocapnia were noted. In only 2 deliberate attempts to hyperventilate the patient excessively did dizziness occur. If the operator is susceptible to hypocapnia mouth-to-mask ventilation should probably be limited to an emergency procedure of fifteen to thirty minutes' duration.

If prolonged mouth-to-mouth ventilation causes hypocapnia in some operators modifications may be employed. Preliminary evidence suggests that for prolonged periods of mouth-to-mask ventilation hypocapnia can be prevented by the imposition of additional external dead space on the operator.

Advantages of the mouth-to-mask method appear to be as follows:

The patency of the patient's upper airway is better ensured, since both hands of the operator are available for support of the mandible and elevation of the patient's tongue and epiglottis. The unpracticed operator is not apt to maintain secure mask fit when he must use one hand to manipulate a bag or a hand bellows.

In inflating the lungs of the patient with expired air the operator unconsciously senses changes in resistance from leaks or airway obstruction. As the operator "feels" the leak or the resistance caused by obstruction or bronchoconstriction, he unconsciously increases expiratory pressure to obtain delivery of the tidal inflation. The prompt and adequate compensations he executes with each breath could not be approached by any automatic cycling resuscitator.

The use of the operator as the power source for a resuscitator has obvious advantages in economy and in speed of initiating artificial ventilation.

The injured patient may be ventilated more promptly, more conveniently, more effectively and with less physical manipulation by the mouth-to-mask method than by any manual method. For the apneic emergency in the patient with tracheotomy, mouth-to-tube insufflation is superior to any method that requires delay or preparation. Obviously, the patient with an injury that interferes with application of a face mask should be ventilated by the mouth-to-tracheal-tube method or by one of the accepted manual methods.[1]

The potential hazard of rupture of the lung in patients with small or abnormal lungs, which must be recognized for all methods of artificial ventilation, may be excluded if inspiratory inflation is terminated when there is perceptible expansion of the chest.

Summary and Conclusions

Mouth-to-mask ventilation was studied in 9 apneic adults. The method appears to be the ideal emergency procedure for artificial ventilation because the patient's alveolar oxygen tension can be rapidly elevated and normal pulmonary gas composition can be rapidly established, no equipment is essential, the most elaborate accessory being a simple face mask (without the mask a mouth-to-nose technic with a handkerchief "filter" is effective.), the operator knows immediately whether the patient is being ventilated, and sufficient inflating pressure is automatically exerted to ensure delivery of an adequate volume, since the operator tends to compensate for changes in airway resistance and in lung compliance.

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THE BIRTH OF QUADRUPLETS, WITH AN ACCOUNT OF THE PLACENTAS AND FETAL MEMBRANES*

ROBERT R. RYAN, M.D.,† AND GEORGE B. WISLOCKI, M.D.‡

EAST WEYMOUTH AND BOSTON, MASSACHUSETTS

THE placentas and membranes of the quadruplets in the case reported below were interesting because they were well preserved, thus affording an opportunity for the preparation of good illustrations and microscopical sections. There are few adequate illustrations of the placentas of quadruplets and quintuplets in the literature, owing partly to their rarity and partly to the fact that some were not preserved and studied whereas others were poorly preserved and still others delivered piecemeal or badly torn.

The placentas and fetal membranes of twins have been the subject of extensive surveys by Guttmacher,[1] and those of triplets by Saniter[2] and Williams.[3] Quintuple births were reviewed by Blécourt,[4] who reported 28 authentic cases in 1904, and by MacArthur and Ford,[5] who in 1937 compiled data on 45 cases. In 1938 Ford and Caruso[6] found 2 further cases in the literature, making a total of 47. Accurate descriptions and illustrations accompanied only a few of these reports. After the birth of the famous Dionne quintuplets, the placentas and membranes were not preserved for study, and no pictures of them exist.[5,7]

Quadruplet births, so far as we know, have not been the subject of any special reviews, the accounts of them and their placentas being for the most part individually scattered in the literature. Quadruplets should occur, according to Hellin's law, once in about 650,000 pregnancies, an estimate approximately borne out by actual statistics.[8] According to expectancy, quintuplets should occur once in every 54,000,000 births.[9]

Statistics on multiple births gathered in the United States for the eight-year period between 1922 and 1930 showed that quadruplet births (both live and still-births) occurred in 37 cases.[10] Hence, in the last hundred years, 300 or 400 quadruple births must have occurred in the United States alone. In view of the relative frequency of quadruplet pregnancies, it is surprising how seldom the condition of the afterbirths has been either described or illustrated.

The sex ratios of series of both quadruplets and quintuplets have been recorded. Five combinations of sexes in quadruplets and six in quintuplets are possible. Hamlett[10] tabulated 48 sets of quadruplets recorded in the United States between 1915 and 1930, with the following sex ratios: 4 males, 13 cases; 3 males and 1 female, 6 cases; 2 males and 2 females, 12 cases; 1 male and 3 females, 7 cases; and all females, 10 cases. In 40 sets of quintuplets in the world medical literature, Newman[9] found the following sex ratios: all males, 8 cases; 4 males and 1 female, 6 cases; 3 males and 2 females, 13 cases; 2 males and 3 females, 2 cases; 1 male and 4 females, 3 cases; and all females, 8 cases. He points out that 23 of the sets of quadruplets, or 48 per cent, and 16 of the sets of the quintuplets, or 40 per cent, consisted of either all males or all females and not, as one would have anticipated, a large proportion of mixed sets and relatively few to be of the same sex. His only explanation for this odd sex distribution was that nearly all the sets of the same sex resulted from fertilization of one egg. On the other hand, from examination of the placentas of a series of 25 triplets Saniter[2] reported that only 2 were single-ovum triplets, whereas 14 were derived from 2 and 9 from 3 eggs.

Newman[9] concluded that with both quadruplets and quintuplets there was a considerable preponderance of males over females — that is, 101:91 among the quadruplets and 110:90 among the quintuplets. However, data compiled by the Metropolitan Life Insurance Company[11] on the sex ratios of plural births in the United States between 1933 and 1941 were at variance both with the data collected by Hamlett for the preceding fifteen years and with the conclusion drawn by Newman. The insurance company's analysis indicated that in the higher orders of plural births females were in the majority: "For triplets there are 101 females born for every 100 males and for quintuplets the ratio is as high as 156 to 100." There appears to be no immediate explanation of these conflicting data and conclusions, and the question should be clarified.

CASE REPORT

A 26-year-old multipara was first examined on January 24, 1952. She had had 3 previous pregnancies and had been delivered of her 1st baby by high forceps. She stated that the 2d and 3d pregnancies had terminated normally, although all the infants were fairly large, weighing between 8 and 9 pounds.

She had had amenorrhea since November 8, 1951, with nausea and emesis at intervals and slight vaginal bleeding. The abdomen was generally tender. Pelvic examination showed the uterus to be enlarged to a size consistent with a 3-month pregnancy. Bed rest was recommended. An ice bag was advised for the abdomen and she was given vitamin E, stilbestrol and amphetamine sulfate. On the following day, when she was seen in consultation, severe congestion in both vaults, with extreme tenderness, was noted. Vaginal varicosities were also observed. Vitamin C, in 50-mg. doses 3 times daily, was prescribed.

*From the South Shore Hospital, Weymouth, Massachusetts, and the Department of Anatomy, Harvard Medical School.

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†Chief, Medical Service, South Shore Hospital; medical examiner, Fourth Norfolk District.

‡Hersey Professor of Anatomy, Harvard Medical School.

On February 13, when she was presumably somewhat over 4 months pregnant, the patient was examined at her home. She had abdominal pain, nausea and vomiting. The nausea was relieved by amphetamine sulfate. During the latter part of February there was moderate vaginal bleeding. The blood pressure was 126/74, and her weight 126½ pounds. In April she noticed signs of the 1st fetal activity. The abdomen became progressively larger. On April 29 her weight had risen to 148 pounds, and her abdomen had markedly increased in size. Serologic study at this time showed that the blood was in Group O, or type 4 Moss, and was Rh positive.

X-ray examination revealed the presence of quadruplets. Fetal development appeared to be normal, and the distal fetus showed a breech presentation.

During May a persistent cough and pain low in the abdomen that was increased by coughing developed. The patient appeared moderately dehydrated, with evidence of congestive changes at both bases. Consequently, she was admitted to the hospital on May 24. She was also having definite uterine contractions. She was given 30 mg. of codeine subcutaneously every 4 hours in an attempt to prevent the contractions and to diminish the coughing. At this time no presenting part could be palpated on rectal examination, and there was no cervical dilatation.

The signs of consolidation in the chest persisted, and x-ray examination demonstrated an atypical pneumonia, with evidence of basal consolidation. This was particularly noticeable in the right lower lobe. On June 17 she had considerable abdominal pain, with marked uterine contractions at brief intervals. When she was removed to the delivery room she was having sustained contractions every 2 minutes. She was given scopolamine, 0.4 mg., and meperidine hydrochloride, 50 mg., but continued to have contractions every 2, 3 and 5 minutes. The contractions subsequently stopped, and she had a fairly restful night.

On June 18 she began having slight uterine contractions. Examination revealed a soft cervix, not completely taken up, with the os dilated to admit 3 fingers. After examination she had a uterine contraction that was sustained for several minutes, and she was moved to the delivery room, where she continued to have mild contractions, which became increasingly stronger. Throughout the day she had a sensation of pressure with intermittent contractions but little evidence of progress as far as cervical dilatation was concerned. Early in the evening she had forceful labor and later in the evening was again removed to the delivery room. The cervix was moderately taken up, and the os dilated to admit 3½ fingers. She was allowed to remain in labor until nearly full dilatation had occurred.

Under spinal anesthesia and after a blood transfusion had been started, the presenting membranes were ruptured, and a breech presented in the right sacroanterior position. After both lower extremities of the fetus had been identified and the umbilical cord, which was coiled around them, had been isolated traction effected the birth of the first baby (a female), who breathed spontaneously, at 10:23 p.m. The umbilical cord of this baby was tagged as "A". Baby "B" presented by the vertex. The membranes of the sac were ruptured, and birth was spontaneous, with moderate pressure from above, at 11:11 p.m.; the cord was labeled "B". Baby "C", another vertex presentation, who was born after rupture of the membranes at 11:24 p.m., cried spontaneously after birth. Its cord was labeled "C". Baby "D" presented as a breech in right sacroposterior position. The membranes were again ruptured, and extraction was accomplished by footling traction. This birth occurred at 11:29 p.m. The baby was extremely pale and apneic. After suction and oxygen had been employed, nikethamide and alpha lobeline administered, and laryngoscopy performed to effect better suction, breathing occurred and was maintained. The baby's color improved. The placentas, which had remained in situ up to this time, were expressed by light pressure (Credé method).

The amount of blood lost was slight. The uterus contracted well after delivery.

There was no laceration of either the cervix or the perineum. The mother was given an additional 500 cc. of blood, and she and the 4 babies left the delivery room in good condition.

The mother made a poor recovery from the anesthesia. She complained of pain in the precordial region accompanied by some shortness of breath. Her pulse rate was somewhat slow, and she became dyspneic. This condition was relieved by the administration of 50 mg. of meperidine hydrochloride, and for a brief period during the following morning she was placed in an oxygen tent, with gradual improvement. She had post-partum pain of moderate severity. She later complained of pain in both lower legs, and although there was no local area of tenderness, the clotting time was determined and she was given 250 mg. of deposolution heparin sodium. On June 13 an electrocardiogram revealed sinus tachycardia with digitalis effect. There was a tendency to low T waves and ST segments, and it was thought that the condition was probably consistent with pregnancy, anemia and myocardial deficiency. A tracing on June 20 demonstrated normal rhythm. Another on June 22 disclosed sinus bradycardia.

On June 22 the mother felt somewhat improved, but her pulse rate remained slow (rate of 58 per minute). It was believed that this was probably a normal cardiac reaction to the strenuous and extended confinement in addition to the respiratory infection and anemia. She gradually improved, continued to gain strength and did not complain of weakness or dyspnea. Her appetite improved, and she had no further nausea. On June 29 her condition was excellent; the lungs were clear clinically as shown by x-ray examination, and the heart sounds were of good quality. She was discharged on that day.

On admission the red-cell count was 2,560,000, with a hemoglobin of 38 per cent (Sahli). There were marked achromia, moderate anisocytosis with macrocytes and microcytes and a moderate degree of poikilocytosis. She was given ferrous sulfate and liver, with only slight improvement in the blood picture. On June 9 the red-cell count had risen to 3,300,000 and the hemoglobin to 40 per cent. She was given blood transfusions, which improved the blood picture only slightly. A week later the red-cell count had increased to 3,570,000, and the hemoglobin to 49 per cent. After delivery, however, and after another transfusion, the red-cell count rose to 4,860,000, and the hemoglobin to 80 per cent.

The infants made good progress. Baby "A" weighed 3 pounds, 5 ounces, on the day of birth, June 18, 1952, and 6 pounds, 3¼ ounces, on the day of discharge from the hospital. Baby "B" weighed 3 pounds, 15½ ounces, at birth and 8 pounds, 5 ounces, on the day of discharge. Baby "C" weighed 3 pounds, 11½ ounces, at birth and 7 pounds, 3 ounces, on the day of discharge. Baby "D" weighed 3 pounds, 9 ounces, at birth and 7 pounds, 10 ounces, on the day of discharge.

The afterbirth of the quadruplets was obtained on June 20 in an excellent state of preservation. It formed a single, large mass, which was not torn or damaged to any significant degree and comprised 4 placentas with fetal membranes attached to one another (Fig. 1 and 2). The entire specimen was fixed in a large quantity of 10 per cent formaldehyde. The total mass weighed 1.931 kg. ("normal" weight in comparison to a normally developed single placenta at full term, which weighs from 500 to 600 gm.).

A numbered label was tied to the placental end of each umbilical cord, giving the sex and sequence of delivery (these data were introduced into Figures 1 and 2). Baby 1, a girl, was born first, followed by 3 boys in the sequence indicated.

The 4 placentas, with their membranes and umbilical cords, observed from the fetal surface, are shown in Figure 1. The umbilical cord of placenta 3 was centrally located, whereas the cords of the others were eccentrically placed near the margins of the placental disks. The cords were well developed and seemingly normal. The lengths of cord attached to the respective placentas were 48, 47, 47 and 43 cm. All 4 cords demonstrated sinistral spiraling. The fetal membranes separating placentas 2 and 4 were noticeably thinner than those separating placentas 1 and 3. Histologic sections through these partitions revealed that the membranes separating placentas 2 and 4 consisted solely of the walls of the 2 amnions fused back to back (Fig. 3), whereas the much thicker partition separating placentas 1 and 3 consisted of chorions and amnions, fused to produce a 4-layered

partition (Fig. 4). The partitions between placentas 3 and 4 and 1 and 2 (Fig. 1) were similarly 4-layered.

The arteries and veins on the surface of placentas 2 and 4 anastomosed with one another, whereas the vessels of 1

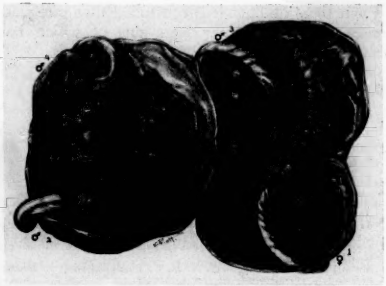

FIGURE 1. *Fetal Aspect of the Placentas and Membranes of the Quadruplets.*

The order in which the babies were born and their sexes are indicated by numerals and symbols placed next to the respective placentas. The placentas of the like-sexed infants 2 and 4 form a single mass with anastomosing blood vessels, the gestation sacs are separated by a relatively thin membrane. Babies 1 and 3, of opposite sexes, appear to possess separate placentas, whose vessels do not anastomose and the walls of whose gestation sacs form a relatively thick partition.

and 3 appeared to be confined within the limits of the respective placentas (Fig. 1).

The specimen from the maternal side (Fig. 2) included 2 placental masses separated by 2 or 3 cm. of membranous

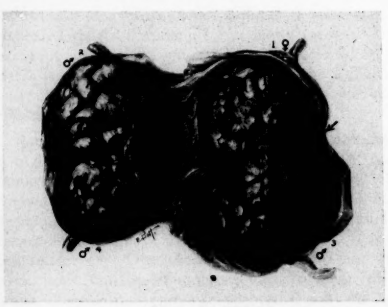

FIGURE 2. *Maternal Surface of the Afterbirth.*

Corresponding parts in Figures 1 and 2 are shown by identical numbers and symbols. (Note the two large separate placental masses.) The mass associated with the twin male infants (2 and 4) was indivisible, whereas that associated with the infants of opposite sexes (1 and 3) broke apart readily, along an irregular seam extending between two notches, which are indicated by arrows in the drawing.

chorion and decidua. The mass comprising placentas 2 and 4 was closely knit and apparently somewhat smaller than that of placentas 1 and 3, which was divided by an inconspicuous but continuous fissure across its middle (the course being indicated by 2 arrows in Figure 2). In the handling of the specimen, placenta 1 separated spontaneously in this plane from placenta 3, demonstrating a natural line of cleavage and indicating that placentas 1 and 3 were merely apposed to one another instead of being integrally united. This was in keeping with the observations that placentas 1

FIGURE 3. *Histologic Section of the Thin Partition Between Placentas 2 and 4 (Gomori's Chrome Alum Hematoxylin and Phloxine Stain X 60).*

The partition consists of two amniotic membranes, fused back to back, without any signs of chorionic membranes.

and 3 were associated with separate chorions, as deduced from study of their fetal surfaces (Fig. 1).

The facts that the disks of placentas 2 and 4 belonged to infants of the same sex, that they were intimately joined with placental vessels coursing from one to the other and that amniotic membranes without chorions intervened between the 2 gestation sacs seem to warrant the conclusion that infants 2 and 4 originated from a single ovum. On the other hand the facts that infants 1 and 3 were of different sexes, possessed separate chorions and the placentas were adherent rather than fused, suggest that each was derived from a separate ovum. Thus, the quadruplets appear to have originated from 3 ova, 1 female and 2 male, with the subsequent formation of identical twins by one of the male zygotes.

The sequence of birth was as follows: first, the female infant, followed by one of the identical male twins, the singleton male and finally the identical male twin.

DISCUSSION

A noteworthy account of the placentas of quadruplets was given by Williams,[3] who described a large, fused placenta with three umbilical cords attached to it and a separate, smaller placenta with one cord eccentrically attached. The entire afterbirth weighed 1.19 kg. A male and 2 female infants were attached to a larger mass, and a female to the separate placenta. The large placental mass was divided into three areas on its fetal surface by three separate chori-

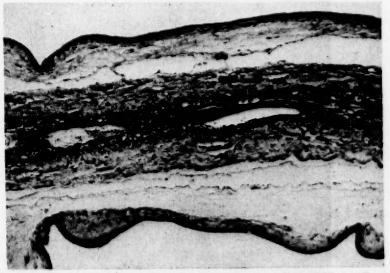

FIGURE 4. *Histologic Section through the Thick Four-Layered Partition between Placentas 1 and 3 (Gomori's Chrome Alum Hematoxylin and Phloxine Stain X 60).*

The two amniotic membranes are separated by two broad chorions facing one another.

ons. Williams concluded that the placenta had resulted from the early fusion of three single ones, and that the quadruplets had originated from four separate ova. His specimen was unusually well illustrated.

Watson,[12] in 1945, reported a quadriovular quadruplet pregnancy in which the afterbirth consisted of a rectangular mass composed of four fused placentas (illustrated by photographs). Each of the four placental units was separated from its neighbors by both an amnion and a chorion. On the fetal surface each cord was eccentrically attached, and the placental vessels did not cross from one placental unit to another. On the maternal surface definite clefts partly separated the placentas. There were 3 females and 1 male. X-ray films, taken at four and a half and seven and a half months, established the diagnosis of quadruplets. (Greenhill[13] cited 4 references to quadruplets demonstrated by x-ray examination up to 1936, and Hamblen, Baker and Derieux,[14] in 1937, presented the first such diagnosis of a quintuplet pregnancy.)

Summary

The course of gestation and the birth of quadruplets to a twenty-six-year-old multipara are described.

The afterbirth consisted of two placental masses each composed of two fused placental disks. One pair of placentas belonged to male twins, who were identical; in this pair the placental blood vessels anastomosed freely between the intimately joined placentas, and the gestation sacs were separated by a partition consisting only of amniotic membranes fused back to back. The other pair of placentas belonged to male and female fraternal twins; in this pair the placental disks were loosely joined, the blood vessels did not anastomose, and the partition between the gestation sacs consisted of both amnions and chorions.

From these findings it is concluded that the quadruplets arose from three eggs, one of which had formed identical twins.

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ORAL ADMINISTRATION OF A POTENT CARBONIC ANHYDRASE INHIBITOR ("DIAMOX")*

I. Changes in Electrolyte and Acid-Base Balance

ALEXANDER LEAF, M.D.,† WILLIAM B. SCHWARTZ, M.D.,‡ AND ARNOLD S. RELMAN, M.D.§

BOSTON

THE dependence of renal acidifying mechanisms on the carbonic anhydrase in the renal tubules is well recognized.[1] The role of this enzyme in acidification of the urine, as well as its function in the production of acid and alkaline secretions in other organs such as the stomach and the pancreas, depends on the catalysis of the reversible reaction: $H_2O + CO_2 = H_2CO_3$.[2] In 1940 Mann and Keilin[3] discovered that sulfanilamide and other unsubstituted sulfonamides inhibit carbonic anhydrase activity, and subsequently the inhibition of urinary acidification by these compounds was demonstrated.[4,5] Even before it had been shown that sulfonamides inhibit renal carbonic anhydrase activity, it had been demonstrated that sulfanilamide produces a diuresis of sodium and potassium in an alkaline urine, which results in the development of hyperchloremic acidosis.[6,7] In 1949, on the hypothesis that the increased cation and water excretion should be of value in the treatment of edema, Schwartz[8] administered sulfanilamide to patients with congestive heart failure. These studies indicated that sulfanilamide frequently increases the excretion of sodium, potassium and water in such patients; however, the clinical use of the inhibitor was discontinued because of the many toxic side effects.

Recently, Roblin and his associates[9,10] synthesized a highly potent, relatively nontoxic inhibitor of carbonic anhydrase (Compound 6063, "Diamox," 2-acetylamino-1,3,4-thiadiazole-5-sulfonamide). Animal experiments showed that Diamox, like sulfanilamide, increases excretion of sodium, potassium, bicarbonate and water.[11-13] Observations by Friedberg and his associates[14] on the intravenous administration of a single dose of this compound to normal subjects and to patients with congestive heart failure also confirmed the earlier findings with sulfanilamide. Similar effects were obtained by Nadell[15] with prolonged oral administration of Diamox.

The present metabolic studies were undertaken with the following purposes in mind: to obtain more complete data on the changes in electrolyte and acid-base balance with oral administration of Diamox¶ to patients with congestive heart failure; to compare the metabolic effects of Diamox and mercurial diuretics; and to determine the relation of dosage to the metabolic response. Succeeding papers[16,17] describe the clinical effects of Diamox in patients with severe congestive heart failure.

METHODS

Six balance studies were done on 5 patients with congestive heart failure and on 1 normal subject. All subjects were maintained on a constant diet. After suitable control observation had indicated stability of weight and electrolyte balance, they were given Diamox by mouth in varying schedules. The chemical methods used and the technics of the balance studies have been described elsewhere.[18,19]

RESULTS

The data are presented in Figures 1 to 6.

The changes in urine and serum induced by Diamox in 3 of the 6 subjects are shown in Figures 1 to 3. Figure 1 demonstrates that oral administration of 250 mg. four times daily to a patient with congestive heart failure produced a prompt inhibition of urinary acidification, indicated by a rise in urine pH and a decrease in excretion of titratable acid and ammonium. Sodium, potassium and water excretion rose. Excretion of nitrogen, phosphorus and organic acids, although not shown in the illustration, was essentially unchanged. In 2 of the subjects there was no change in chloride excretion (Fig. 1 and 3), which increased in the third (Fig. 2), however. The excretion of this alkaline urine resulted in slight weight loss and the development of systemic hyperchloremic acidosis, with elevation of serum chloride

*From the medical services, Massachusetts General Hospital, New England Center Hospital, and Evans Memorial, Massachusetts Memorial Hospitals, and the departments of medicine, Harvard Medical School, Tufts College Medical School and Boston University School of Medicine.

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†Associate in medicine, and Howard R. Hughes Fellow in Medicine, Harvard Medical School; assistant physician, Massachusetts General Hospital.

‡Assistant professor of medicine, and Markle Scholar in Medical Sciences, Tufts College Medical School; assistant physician, New England Center Hospital.

§Assistant professor of medicine, Boston University School of Medicine; associate member, Evans Memorial, Massachusetts Memorial Hospitals.

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concentration and reduction in serum carbon dioxide content and pH. Serum sodium and potassium concentrations were unchanged. Promptly on cessation of therapy, chloride excretion rose, and the initial changes in urinary excretion were reversed: sodium and potassium excretion fell, whereas excretion of acid (in this case, largely ammonium) increased. As a result the serum pH and the concentrations of bicarbonate and chloride returned to control levels (Fig. 1 and 3).

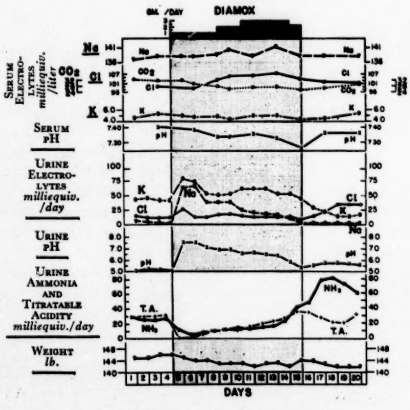

FIGURE 1. *Effect of Diamox on Serum Electrolyte Concentrations, Urinary Electrolyte Excretion, Body Weight, and Urine and Serum pH in Case 1, a Sixty-Three-Year-Old Man.*

Note that sodium and potassium excretion increased, without change in urine chloride, as hyperchloremic acidosis developed in the serum. Intake was constant and, by analyses, consisted of 29 milliequiv. of sodium, 52 milliequiv. of potassium, 32 milliequiv. of chloride, 8.7 gm. of nitrogen and 1345 cc. of water. Stool sodium and chloride content remained constant at 1.0 milliequiv. per day. Stool potassium, which was 17 milliequiv. per day during the control period, dropped to 8 milliequiv. per day during Diamox therapy and then rose again to 16 milliequiv. per day. Stool nitrogen was 1.1 gm. per day during the control period, 0.5 gm. daily during treatment and finally 0.9 gm. per day.

It was noted that despite continuous administration of Diamox, urinary excretion reverted to the pattern of the control period. For example, urinary pH and the sodium, potassium, titratable acid and ammonium excretions had gradually returned to control values by the last day of treatment (Fig. 1). However, the hyperchloremic acidosis produced initially persisted throughout the treatment period. The diminishing effect of continuous treatment on urine electrolyte excretion was not overcome by an increase in dosage up to 2.5 or 3.0 gm. per day (Fig. 1). The development of resistance to continuous therapy is also apparent in Figures 2 and 3. As might have been expected diuresis and weight loss were greatest at first and then waned with the diminishing excretion of electrolytes. The relation between electrolyte excretion and weight loss is most effectively demonstrated in Figure 3.

Resistance to the diuretic action of Diamox appeared to develop in Case 3 after a single dose of 250 mg. The initial degree of responsiveness was not restored even with intervals of one or two days between single doses. Figure 3 shows that the first response to a single dose of 250 mg. was approximately the same as that produced initially by the same dose given four times daily.

In 3 patients with congestive heart failure (Fig. 4-6) there was no significant sodium diuresis although urinary acidification was inhibited. In 1 of these (Fig. 4) there was an equivocal increase in urinary potassium, and in another (Fig. 5) there was a definite potassium diuresis on two occasions, but neither subject lost sodium or weight. In the third subject (Fig. 6) potassium excretion increased slightly, but weight loss was greater than would have been predicted from the cation loss observed. Increased uri-

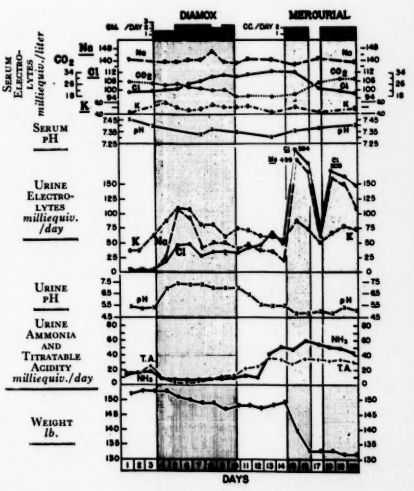

FIGURE 2. *Effect of Diamox and Mercurial Diuretics on Serum Electrolyte Concentrations, Urinary Electrolyte Excretion, Body Weight and Urine and Serum pH in Case 2, a Sixty-Seven-Year-Old Man.*

Note that sodium excretion exceeded that of chloride during the Diamox period but that chloride exceeded sodium during mercurial diuresis. Diamox produced hyperchloremic acidosis, and mercurial diuretics had the opposite effect. During the period of mercurial treatment the scale for urine sodium and chloride was interrupted.

nary volume and rise in serum sodium concentration indicated that this weight loss was probably due to water diuresis.

Cases 2 (Fig. 2) and 6 (Fig. 6) were given mercurial diuretics after treatment with Diamox to

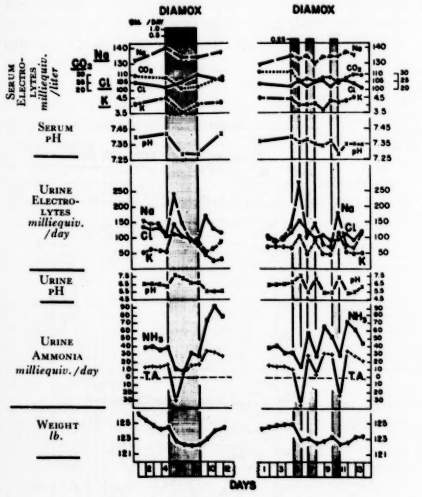

FIGURE 3. *Effect of Diamox on Serum Electrolytes and Urinary Electrolyte Excretion and Body Weight in a Normal Subject (Case 3, a Twenty-Six-Year-Old Woman).*

The first course of therapy illustrates the prompt development of resistance to the drug. Four days of continuous treatment had no greater total effect than the first single dose during the second course of treatment. Intervals of one and two days between single doses failed to restore the initial state of responsiveness.

contrast the actions of these two agents. Both patients had a diuresis of a large amount of chloride, accompanied mainly by sodium, and a small quantity of ammonium. These electrolyte losses resulted in a fall in serum chloride concentration with a reciprocal rise in serum carbon dioxide content and a small increase in serum pH. Weight loss in both cases was considerably greater than that produced by Diamox.

DISCUSSION

The sequence of events after administration of a carbonic anhydrase inhibitor has been described by previous workers[7,13-15] and is similar to the typical results observed in 3 of our 6 subjects (Fig. 1, 2 and 3). Inhibition of carbonic anhydrase activity in the renal tubule results in a lower rate of secretion of hydrogen ions.[5] In consequence urinary pH increases, ammonium and titratable acid excretion falls, and the urine contains larger amounts of sodium, potassium and bicarbonate. This loss of bicarbonate salts increases water excretion and produces hyperchloremic acidosis in the serum. It was noted by us, as well as by others,[7,13,15] that these urinary changes occur only at the beginning of treatment and that with continuous administration of the inhibitor the composition of the urine reverts to pretreatment values.

The rapid development of unresponsiveness to repeated use of the drug, even with intervals of one or two days between doses, appears to limit the usefulness of Diamox as a diuretic. In the present studies drug resistance was always associated with the appearance of hyperchloremic acidosis. In acute ani-

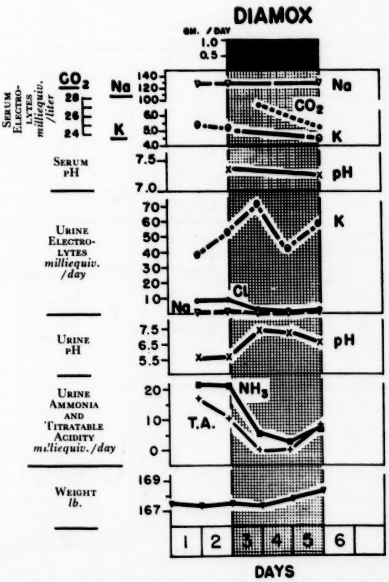

FIGURE 4. *Effect of Diamox in Case 4, a Sixty-Three-Year-Old Man.*

This edematous subject failed to lose weight or sodium. That Diamox was having a definite effect on the kidneys is indicated by the changes in urinary pH, ammonium and titratable acid excretion and by the equivocal increase in potassium excretion.

mal experiments the bicarbonate diuresis that follows intravenous injection of drug has been found to be directly proportional to the initial serum bicarbonate concentration.[12] Thus, the development of acidosis, resulting from the initial urinary loss of alkali, might have been expected to restrict diuresis further. In this sense the action of the drug is self-limiting.

Analysis of the urine several days after institution of treatment, when urinary composition had been re-

stored to its control values, might have suggested that the kidney was no longer under the influence of the drug. However, the persistence of acidosis during treatment and the subsequent correction of the acidosis on cessation of treatment clearly indicated that the mechanism for acidification of the urine had been under continuous, although partial, inhibition. The apparent recovery of the renal acidification processes, with the development of resistance, does not necessarily mean that hydrogen ion transport had been restored to its control rate. The reduction in filtered bicarbonate resulting from the initial bicarbonate diuresis would obligate less hydrogen ions in the reabsorption of bicarbonate and might therefore permit restoration of titratable acid and ammonium excretion with the same reduced over-all exchange of hydrogen.

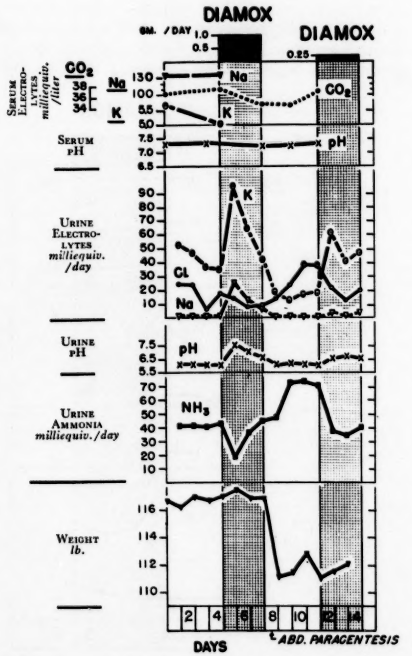

FIGURE 5. *Effect of Diamox in Case 5, a Forty-Nine-Year-Old Man with Congestive Heart Failure Who Lost Potassium but Had No Significant Diuresis of Sodium and No Weight Loss.*

The large weight loss shown on the figure was due to an abdominal paracentesis on the eighth day of the study.

It is interesting that no subject lost sodium without potassium, the range of the potassium loss being the same in those who lost sodium as in those who did not. These facts suggest that when hydrogen transport is inhibited in subjects with congestive heart failure, potassium is the cation most readily available for execretion, and that sodium diuresis begins only after the readily available potassium has been excreted. This initial preferential loss of potassium has been observed in other situations in which there is obligatory urinary loss of anion in the presence of sodium retention.[20-23] Despite the regular occurrence of potassium loss, neither hypokalemia nor clinical evidences of potassium deficiency was observed. In addition to his potassium loss Case 6 experienced an unexplained loss of water in excess of fixed cation (Fig. 6).

It is significant that in the doses used this drug usually failed to produce a large augmentation of

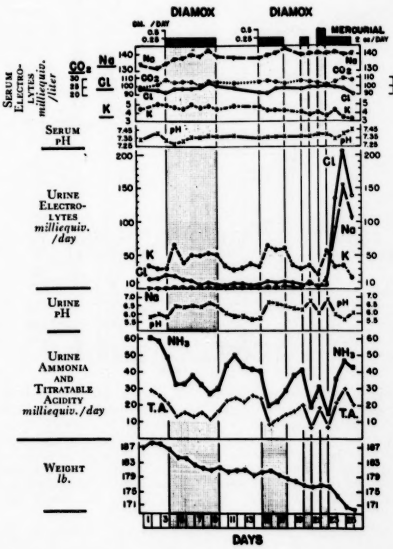

FIGURE 6. *Effect of Diamox in Case 6, a Thirty-Eight-Year-Old Man.*

On two occasions administration of Diamox produced no sodium loss but was associated with a water diuresis as evidenced by weight loss and a rise in serum sodium concentration. The administration of mercurial diuretics caused large losses of sodium and chloride, with a significant weight loss.

chloride excretion either during therapy or on the first day or two after treatment had been stopped. Any substance that will exert a continual, effective diuretic action must produce a significant loss of chloride. Loss of sodium or potassium as bicarbonate can, theoretically, result at most in excretion of a proportion of the extracellular fluid no greater than the proportion of extracellular anion that is bicarbonate. Obviously, such a reduction of bicarbonate would not be tolerated.

There are two mechanisms through which acidosis and drug resistance might be avoided. Excretion of sodium chloride would tend to maintain the serum bicarbonate concentration by reducing extracellular fluid volume. In the present study none of the subjects excreted enough chloride to defend the bicarbonate level in this way. An alternative mechanism for the restoration of serum bicarbonate is the excretion of ammonium chloride in the interval between doses. None of the dosage schedules tested produced this theoretically most optimal result. A longer interval between doses than that tried here might permit complete regeneration of serum bicarbonate and restoration of responsiveness to the drug; however, infrequent diureses of the modest proportions seen in the present studies would be of minor therapeutic value to the severely edematous patient.

TABLE 1. *Comparison of the Effects of Three Different Diuretic Agents on Serum and Urine.*

AGENT	SERUM	URINE
Diamox	Hyperchloremic acidosis	Alkaline
Ammonium chloride	Hyperchloremic acidosis	Acid
Mercurial diuretic	Hypochloremic alkalosis	Acid

It is interesting to compare the effects of three different diuretics (Diamox, ammonium chloride and mercurials) on the acid-base balance of serum and urine. Table 1 summarizes the important changes. Ammonium chloride and Diamox are similar in that they produce a hyperchloremic acidosis in the serum, but ammonium chloride accomplishes this by the addition of hydrochloric acid to the blood whereas Diamox removes sodium bicarbonate in the urine. The urine is alkaline during Diamox therapy and acid during ammonium chloride administration. Mercurial diuretics cause excretion of acid urines high in chloride, with a resulting tendency to a hypochloremic alkalosis of the serum.[20]

SUMMARY

Balance studies were carried out in 5 subjects with congestive heart failure and in 1 normal subject during administration of Diamox, a potent inhibitor of carbonic anhydrase activity.

In 2 subjects with congestive heart failure and in the normal subject the responses were similar to those previously observed after administration of sulfanilamide. These effects included excretion of an alkaline urine containing increased quantities of sodium and potassium, and the development of hyperchloremic acidosis. Three other subjects lost no sodium and responded to the drug only with reduction in urine acidity and increased excretion of potassium. In no case did significant hypokalemia or clinical signs of potassium deficiency appear.

None of the patients studied excreted sufficient chloride during treatment to prevent the prompt development of hyperchloremic acidosis and drug resistance. Intervals of six to forty-eight hours between single doses were insufficient to allow regeneration of serum bicarbonate through the renal excretion of an acid urine. Despite the loss of diuretic action during continued administration of the drug, the data suggest that the drug maintained an inhibitory effect on renal acidifying mechanisms.

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DEFECTIVE BLOOD COAGULATION FOLLOWING PULMONARY SURGERY*

S. Randolph Penn, M.D.,† and James H. Walker, M.D.‡

BOSTON

It is the purpose of this paper to present 2 cases in which massive hemorrhage due to an abnormality in the clotting mechanism occurred immediately after pulmonary resection. In 1 case the condition was recognized promptly, and the intravenous use of fibrinogen§ was followed by restoration of a normal clotting time and cessation of bleeding.

Case Reports

Case 1. S.C.L. (N.E.D.H. 42078), a 52-year-old housewife, was admitted to the hospital with a complaint of cough productive of purulent sputum. She had undergone partial thyroidectomy, tonsillectomy, resection of the nasal septum and removal of a benign cyst of the breast between the ages of 15 and 42, without evidence of undue bleeding. An elevation of the blood pressure had been present for 2 years.

Physical examination was negative except for kyphoscoliosis, a blood pressure of 190/100 and rales in the left-lower-lung field posteriorly.

Examination of the blood showed a hemoglobin of 12 gm. per 100 cc. and a white-cell count of 6250 with a normal differential. The blood sugar was 97 mg., and the nonprotein nitrogen 17 mg. per 100 cc. The blood Hinton test was negative. The urine was normal.

Bronchographic examination established the diagnosis of bronchiectasis involving the left lower lobe.

At thoracotomy on April 13, 1953, there were no pleural adhesions. The left lower lobe was resected, followed by a sympathectomy extending from the lower end of the stellate ganglion through the 11th thoracic segment, with the removal of the greater, lesser and the least splanchic nerves and a portion of the celiac ganglion. Hemostasis was satisfactory. During the operation, which lasted 2¾ hours and was uneventful, the patient received 1000 cc. of bank blood and 1000 cc. of 5 per cent glucose in water. The blood pressure had fallen to 110/80 and the pulse rate, previously 110, to 90 at the end of the operation. She was returned to her room in excellent condition.

Two and a half hours later the systolic blood pressure suddenly dropped to 70. The pleural drainage was quite bloody. A transfusion of bank blood was started, and 2 cc. of methoxamine hydrochloride was given. During the next 6 hours 4500 cc. of bank blood was administered in addition to 2000 cc. of 5 per cent glucose in water. Blood, however, continued to accumulate in the pleural-drainage bottle. The chest was reopened 12 hours after the 1st operation. Many blood clots were found within the layers of muscles as well as within the thoracic cavity. The wound was thoroughly irrigated and explored, but no major bleeding points were found. Oozing from the entire wound then began, and it was noted that this blood failed to clot; 4500 cc. of blood was given during the operative procedure.

A fibrinogen deficiency was considered at this time, but fibrinogen was not available until near the completion of the operation, when 4 gm. was given intravenously. The blood pressure was then 130/80; the patient's color and pulse were good, the skin was warm and dry, and for the first time clotting was noted in the drainage bottle. The patient regained consciousness and was returned to her room. Within 30 minutes tracheal secretions began to accumulate, and she became cyanotic in spite of nasal administration of oxygen. The systolic blood pressure dropped to 80, and the pulse was feeble and rapid. Tracheal aspiration recovered pure blood from the tracheobronchial tree. A tracheotomy was carried out in bed to facilitate aspirations. The respirations improved, but fresh bloody secretions reaccumulated and she suddenly became cyanotic and died. Autopsy was not performed.

Case 2. W.E.C. (B.V.A.H. 8739), a 36-year-old mail carrier, was admitted to the hospital complaining of coughing up of bright-red blood for 2 days. After an episode of "pneumonia on the left" 10 years previously he had had recurrent episodes of fever, with pain in the left mid-lateral aspect of the chest, and a chronic cough productive of half a cupful of purulent sputum daily.

Physical examination was negative except for dullness and decreased breath sounds over the left-middle-lung field posteriorly. There was no clubbing of the fingers.

Examination of the blood revealed a hemoglobin of 13.5 gm. per 100 cc., a hematocrit of 45 per cent and a white-cell count of 14,050, with a normal differential. The blood Hinton test was negative. The urine was normal. Examination of 3 sputum specimens was negative for acid-fast bacilli and neoplastic cells.

X-ray study of the chest showed an area of consolidation in the region of the superior segment of the left lower lobe, with moderate emphysema of the remaining portion of the lower lobe. (Bronchograms taken 4 years previously demonstrated saccular bronchiectasis of the superior segment of the left lower lobe.) Marked edema and granularity of the mucosa about the orifice of the left superior segmental bronchus were seen on bronchoscopic examination.

At thoracotomy on May 14, 1953, the visceral and parietal pleural surfaces were found to be completely sealed, extensive dissection to mobilize the lung being required. The superior segment of the left lower lobe, which was consolidated and contracted, was removed after the hilar dissection and division of the superior segmental artery, vein and bronchus. The patient received 2500 cc. of bank blood, which was estimated to be adequate replacement for the considerable amount of blood loss. The lung was re-expanded, hemostasis was achieved, and the chest was closed without incident. The operating time was 3½ hours. The blood pressure was 110/70 at the end of the operation, having ranged between 110/60 and 90/60 during the procedure.

*From the Surgical Service, Boston Veterans Administration Hospital, and the New England Deaconess Hospital.

†Formerly, resident in surgery, Boston Veterans Administration Hospital, and chief of surgery, Cushing Veterans Administration Hospital, Framingham, Massachusetts.

‡Thoracic surgeon, Charleston Memorial Hospital, Charleston, West Virginia; formerly, instructor in thoracic surgery, Tufts College Medical School, thoracic surgeon, New England Deaconess Hospital, and attending thoracic surgeon, Boston Veterans Administration Hospital.

§Kindly supplied by Dr. Louis K. Diamond, of the Children's Hospital, Boston, through the American Red Cross.

The patient was returned to the ward in good condition. Four hours after the operation the blood pressure suddenly fell to 40/20, the pulse became rapid and weak and the respirations shallow, and the extremities were cool and moist. A transfusion of bank blood was started through an intravenously inserted cannula, and blood taken at that time showed a hemoglobin of 9.8 gm. per 100 cc. and hematocrit of 33 per cent; 2 cc. of levarterenol bitartrate was given intramuscularly, and 2 cc. added to the transfusion. X-ray films of the chest taken with a portable machine showed the lung to be well expanded, with no evidence of fluid. The drainage catheters were working well and had drained about 250 cc. of bloody fluid.

During the next 6 hours 3000 cc. of bank blood containing 8 cc. of levarterenol bitartrate was administered. The blood pressure was maintained throughout this period at about 80/60. The general condition improved; the pulse slowed to 110 and became more full. Breath sounds were audible throughout the left lung. By then about 600 cc. of blood had drained into the suction bottle. The hemoglobin and hematocrit were 10.3 gm. per 100 cc. and 34 per cent. Blood clotting by the 2-test-tube method took 33 minutes, with a clot that was easily fragmented by gentle agitation. Ninety minutes after the intravenous administration of 4 gm. of fibrinogen the clotting time was 3 minutes.

During the next 10 hours an additional 3000 cc. of whole blood was given (1000 cc. of which was less than 18 hours old). The blood pressure remained at 90/70, with a pulse rate of 110. The breath sounds over the left lung became less audible, and the trachea appeared deviated to the right; dyspnea developed. X-ray examination revealed generalized clouding of the left side of the chest, with deviation of the mediastinum to the right. The clotting time had risen to 12 minutes, the hemoglobin remaining at 10.4 gm. per 100 cc. and the hematocrit at 36 per cent. An additional 4 gm. of fibrinogen was given intravenously. One hour later the clotting time was 4 minutes.

Twenty-four hours after the completion of the 1st operation and after the administration of 10,000 cc. of blood, the wound was reopened and approximately 2000 cc. of clotted blood was removed from the pleural cavity. A thorough search was made for actively bleeding vessels; none were found. The operative field was irrigated with warm saline solution, the lung re-expanded, and the wound closed.

The postoperative course was satisfactory. The patient was out of bed and walking on the next day. The wound healed well, and the sutures were removed on the 8th postoperative day. He was discharged from the hospital 12 days after the 1st operation.

Discussion

Major hemorrhage due to a defect in blood coagulation is a rare complication of surgery, but is probably more common after operations on the lung than in other fields.[1,2] Mathey et al[1] considered the drastically lowered fibrinogen levels in a series in which severe bleeding followed pulmonary resection to be due to abnormal fibrinolytic activity. Hidalgo, Fowell and Ralls[3] showed that in rabbits extensive tissue damage was followed by a significant decrease in the plasma fibrinogen within six hours. Stefanini[4] regarded fibrinolysis as responsible for bleeding more frequently than is commonly recognized; he noted that the uterus and lung were particularly rich in kinases, which may activate fibrinolysin "in vivo" should they gain entrance into the circulation.

Obvious bleeding tendencies might be detected preoperatively by determinations of the bleeding and clotting time, the prothrombin time and the platelet count. Defects in blood coagulation, however, followed by hemorrhage, may occur even though preoperative studies reveal no abnormality. Determination of the blood clotting time and a study of the clot itself are of aid in establishing the cause of the bleeding. Although other factors may cause a prolonged clotting time and a clot that is easily fragmented, the defect may result from fibrinolysis, when fibrinolysin is activated by tissular material (kinase) that enters the circulation or insufficient production of fibrinogen by the liver to compensate for the increased need or both. In either of these events fibrinogen should be given.[5] Acquired afibrinogenemia or hypofibrinogenemia is probably not an unusual occurrence after major surgery, but the level of fibrinogen rarely falls so low that serious bleeding results.[5]

Summary

Two cases of major hemorrhage due to the development of a blood coagulation defect after pulmonary resections for bronchiectasis are presented.

In 1 case the defect was not recognized promptly, and secondary exploration was performed. No bleeding vessel was found, and the patient died.

In the other, in which the clotting defect was recognized promptly, fibrinogen was administered intravenously. The clotting time became normal, and the bleeding ceased. After supportive treatment, a second operation was performed to evacuate the hemothorax. The patient made a good recovery.

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SPECIAL ARTICLE

CHOICE OF OPPORTUNITIES IN MEDICINE*

JAMES HOWARD MEANS, M.D.†

BOSTON

To the young man or woman who has just earned the degree of doctor of medicine a rich spectrum of opportunity presents itself. As some years earlier the choice of medicine as a career had to be made, so now again a choice has to be made—this time that of what area of medicine the young doctor shall enter. No longer can anyone encompass it all. Some may select a relatively wide portion of the spectrum, others may focus sharply on one of its narrower bands, but never should any of them let the light of the whole fade entirely from the field of his professional sensibility.

In making his choice the young doctor must have in his mind some understanding of the over-all nature of medicine and of its place and function in the total social order. Also, he must practice some self-scrutiny to identify as best he can his own motivations, interests and skills. He must think in terms of what variety of medical work he can do best and of what kind has the most attraction for him. The greatest rewards of any professional work lie in the satisfaction of doing it well and of extending the boundaries of what it can accomplish. Medicine is and should be—for the good workman is worthy of his hire—a well paid profession, but no one should embrace it whose primary objective is mercenary.

Broadly speaking, medicine nowadays can be said to be one of the great sinews of the social organism. It has the function of promoting, preserving and restoring the health both of persons and of communities. In such a capacity it has in its hands the manpower of a nation. This total function can be subdivided in various ways. One way would be into the practice of medicine, medical education and medical research. Practice in the traditional sense means care of the patient. Today, however, one hears the term "public-health practice" used with increasing frequency—the routine work of the health officer, who seeks to do for the community what the practitioner of medicine does for individuals.

The main purpose of this discussion is to serve as a guide to the practice of medicine as it applies to the individual, but according to my own philosophy the practice of medicine in its broad aspects is inextricably bound up with education and research. Without research there is no progress, and without education there are no new doctors. Every physician must always seek ways of imparting his skill and use his powers of observation to uncover new facts. Of recent years certain doctors of medicine have devoted themselves more exclusively to teaching and research than to practice, but if they are doctors of medicine they should engage to some extent in the care or problems of patients, because otherwise they will cease to be competent to teach medicine or to recognize the questions that medicine needs to have answered.

General Medicine and Surgery

Doctors primarily engaged in the practice of medicine can be divided, to some extent, by the broad nature of their approach to the care of patients, into physicians, surgeons and psychiatrists or, by what portion of the whole content of medicine they seek to cover, into specialists and generalists, still commonly called general practitioners. The propriety of equating the role of the psychiatrist with those of the physician and surgeon will be challenged by many, but plenty of evidence to justify such an appraisal is accumulating. William C. Menninger has well pointed out that the anatomy of the personality is no less a concern of the doctor than the anatomy of the body. That this concept is not entirely new is witnessed by the fact that Robert Burton wrote in 1621 on the "Anatomy of Melancholy." Nevertheless, Dr. Menninger is fully justified in pointing out that the present-day medical profession is insufficiently aware of it. Moreover, in dealing with the problems of the personality, a wealth of new knowledge undreamed of until the beginning of the work of Freud only sixty years ago is available.

The young doctor of today at graduation time is confronted merely with the choice of which of these general approaches to practice he will follow. Indeed, he need not make even this choice until later because before him lie one or often several years of graduate training in hospital house-staff jobs, during which his inclination will be clarified. Certainly, his choice of a narrow clinical specialty may be deferred until well along in the house-staff training or even later.

The majority of internships offered by American hospitals at present are of the mixed or rotating type. They encompass brief bits of practical training in a variety of fields of medicine. A single year of such experience is hardly adequate training even for the

*Adapted from the chapter entitled "Choice of Opportunities" in the forthcoming book, *The Physician, His Practice and His Business*, by permission of the publishers, Little, Brown and Company.

†Physician to Massachusetts Institute of Technology; Jackson Professor of Clinical Medicine, emeritus, Harvard Medical School; formerly, chief, Medical Services, Massachusetts General Hospital.

most general of general practices. Yet it is all that a certain portion of medical graduates are getting in the United States today. As a prelude to assistant residencies and residencies more specialized in scope, however, the one-year rotating internship is often quite satisfactory.

A minority of hospitals, but from the training point of view among the best, require from the very start a choice between medicine and surgery. They offer straight services in medicine on the one hand and in surgery on the other. The graduate who chooses such a straight service has usually decided at least whether he wishes to become a physician or a surgeon. There are exceptions as when, having finished a straight medical internship, the physician then switches to surgery. This is a good program if he can afford the time. I even know of cases in which graduates of straight surgical internships ended up as psychiatrists.

For the purpose of making a primary choice between medicine, surgery and psychiatry, the graduate must know something of the nature of these callings and what it takes to serve them. The traditional separation of members of the medical profession into subspecies is into physicians and surgeons. Psychiatrists, as such, came later. The contrast between physician and surgeon is exemplified by such terms as "College of Physicians," "College of Surgeons" and "College of Physicians and Surgeons." That two callings are involved is also implied by the signs of doctors of medicine who proclaim to the public that they are both "physician and surgeon." There is no difficulty about the term "surgeon." He is one who treats the sick by means of the knife; his is a special approach, and he himself is a specialist. The term "physician," however, is more nebulous. Doctor Johnson's famous dictionary (1755) gives the following definition: "Physician—one who professes the art of healing." This definition obviously includes the surgeon, who is a subspecies of physician. Two hundred years later a modern dictionary of "American English" states, "Physician, (a) One who practices the art of healing (obsolete) and (b) One legally qualified to practice medicine—often distinguished from a surgeon." It is in the latter sense that I like to use the term "physician." I consider that that is what I am myself. It means that I have some competence for caring for the patient, but none at all for doing surgical operations or of carrying out the special technics of a number of narrow specialties. There is justification for such a course even in the oath of Hippocrates, in which it is said, "I will not use the knife, not even verily on sufferers from stone, but I will give place to such as are craftsmen therein."

The personality traits and aptitudes that go to making the good physician differ from those that are needed in the make-up of the good surgeon. The surgeon performs in the limelight. He is the virtuoso of medicine. His professional work consists to a considerable extent in dealing with crises. At least to the patient the surgical operation is a crisis. The surgeon, who enters and often leaves the patient's life at this time of crisis, in a sense is always on the spot. He must make vital decisions with great rapidity. He must know his way around inside the human body with utter accuracy, certainty and confidence. He must be a robust, resilient, psychologically extroverted sort of person. If he did not have such qualities he could not take what the surgeon has to take.

The function of the physician is quite different. He is less concerned, at least if he is of the category that I have called "generalist," with crises than with the sustained care of patients, keeping them well if he can, or trying to restore them to health if they become sick. He applies any sort of treatment that he is qualified to give and calls in specialists when skills beyond his competence are indicated. The qualities required to make a good physician are understanding, insight, purposeful sympathy, responsibleness and patience. Also, his personality must be one to inspire confidence. He is not on the spot as the surgeon is, and can more readily admit error without losing either face or patient, provided the patient has trust in him. His concern is with the whole patient. He is indeed the personal physician.

The specialist occupies an intermediate position between the physician and the surgeon in the sense in which I have used these terms. Often, he retains charge of patients for long periods, but he is only taking care of a part of them. The difference, as I see it, between the three categories of practitioners of medicine that I have mentioned is that the surgeon is interested primarily in the operation and the specialist in the disease, but the nonspecialized physician or generalist is interested primarily in the person.

Psychiatry

Before opportunities in the narrower clinical specialties and nonclinical opportunities in medicine are outlined the role and place of psychiatry in the medical spectrum should be indicated. Is psychiatry a specialty? Most people would say yes, of course, but I think it is not completely so. It is a specialty in that it uses specialized technics and requires long and special training, but in its field of operation it is hardly a specialty since it deals with the whole height, depth and breadth of the human personality. Except for pediatrics and geriatrics, which are general medicine applied to particular age groups, the clinical specialties are focused on organs, diseases or technics, not on persons. Psychiatry, on the other hand, is most assuredly focused on persons, on personalities, in fact —so much so that the psychiatrist, though always a doctor of medicine, may sometimes miss an organic process that is perhaps causing no symptoms or erroneously interpret symptoms as of purely psychic origin that actually result from primary organic disease. The psychiatrist, being a graduate in medicine,

is competent, by training, to examine the patient completely in body as well as mind, but usually he depends on the physician to take care of the former.

The objectives of psychiatry have broadened greatly in the last few decades, and to the medical graduate of today this specialty offers a wealth of opportunity for interesting professional work undreamed of at the turn of the century. Fifty years ago diagnosis in psychiatry amounted to not much more than the taxonomy of lunacy, and its therapeutics consisted of custodial care in a mental hospital or sanatorium. Today, the situation has considerably improved. The modern psychiatrist's first objective is to keep people mentally well. To a great extent his has become largely an office instead of an institutional practice. The stigma of psychiatry is becoming dispelled from the minds of the people. Patients seek voluntarily the services of psychiatrists when faced with emotional problems that they have difficulty in resolving. The discipline has shifted from a negative to a positive approach in the care of patients.

What it takes to make a good psychiatrist is similar to what is required for the nonspecialized physician. But certain traits must be more intensely cultivated. The ability to attain to great objectivity and patience is paramount. Also, there must be deep and genuine interest in people as persons, and in the dynamics of human relations. Intellectual capacity and general education sufficient to permit understanding and communication with highly intelligent people are likewise essential.

The psychiatrist's life can be more regularly ordered than that of most other practitioners. Except when he is called out to deal with an acutely psychotic patient (which, of course, can be a taxing business) his work can be ordered and scheduled by the clock just as he pleases. By common consent when the psychiatrist is with his patient he is incommunicado, whereas the ordinary doctor is expected to answer the telephone regardless of what he is doing.

Internal Medicine

Just what is the internist? To the laity the term is largely meaningless, or it may be confused with intern. Despite the fact that the root word in one case means inside the patient and in the other inside a hospital, a recent standard American dictionary actually gives intern as synonymous with internist! In most general dictionaries the word internist cannot be found at all. Only in the medical dictionaries can one find it, and even then the definition is apt to be disconcerting,—for example, "one who treats internal diseases: a physician distinguished from a surgeon,"—but does not the surgeon treat internal diseases, and does not the internist sometimes treat external ones? To be sure, there is a specialty board in internal medicine, but does that make the internist a specialist?

Perhaps the best approach is to observe what he does, after which it may appear that there is little sense in calling him an internist. In actual practice one finds so-called internists heavily engaged in diagnostic work, much of it in consultation with general practitioners, treating patients with a wide variety of diseases or referring them to physicians in the narrower specialties for care beyond the scope of internal medicine. In fact, then, it seems to me that the internist is nothing more nor less than the nonspecialized physician, whose practice I have already defined, but with a specialist's rating. Personally, I much prefer the term physician to that of internist, an exotic word imported some decades ago from Germany. I find, moreover, that my British medical colleagues share this preference.

Other Clinical Specialties

Of the narrower clinical specialties as career opportunities in medicine, certain general statements may be made. Knowing more and more of less and less is the bromidic remark that is often made of them. It is very unseemly, however, to disparage them, for they are absolutely essential if all that medical science has to offer is to be made available to the patient: difficult and special technics are often required in either diagnosis or treatment. Many doctors find complete contentment in the practice of these specialties, which may become intellectually satisfying, particularly if, together with care of patients, they include some research and teaching.

All clinical specialties presuppose an adequate clinical training in general medicine, and many of them—for example, ophthalmology, otolaryngology, urology, proctology, gynecology, obstetrics and orthopedics—require a good grounding in general surgery as well. Such nonoperative specialties as neurology, dermatology, allergy, cardiology, endocrinology, gastroenterology and radiology need only a preceding general medical experience. The recent graduate must first get his general clinical training and then embark on his training for a specialty. It is a lengthy progression, but a great many are eager to follow it. The older and well established specialties all have certifying boards, which lay down certain minimum training requirements for certification; although there is no legal mandate that the specialist must receive his board certification before practicing his specialty, the weight of professional opinion is such that he will have tough going without it.

In addition to the more formal and traditional specialties, there are cropping up all the time new ones that start off merely as special interests within a broader field. A general physician, or an internist, may become interested in some special clinical problem,—a certain disease perhaps,—on which he makes himself an authority. He does not limit his practice to it, but if he gains a reputation in it he is consulted by other doctors who think he may have something

special to contribute in some of their cases. Thus, many generalists will also be informal specialists in a field that has particular interest for them. And this is altogether desirable. The special interest is challenging and often seems to keep the generalist more alert to medical progress than he would be without it. General surgeons too often gain particular skill in some highly specialized procedure but at the same time do not want to confine their work to it, nor is such a limitation desirable.

In making up his mind what variety of medical practice he will engage in the doctor of today has many questions to consider, not only whether he will be generalist or specialist, but also in what sized community he will settle, and whether he will practice by himself or as a member of a practice group. Solo practice of medicine is the traditional pattern, but with the growing complexities of modern diagnosis and treatment, teamwork of some sort for the provision of medical care is becoming ever more important. Solo practitioners, generalists and specialists, collaborate to provide complete medical care to patients, which may, however, be less effective and more costly to the patient than that obtainable from an organized practice group. A great variety of groups already exist in the United States, and there is considerable evidence that many of the younger doctors are glad to join them. There is much satisfaction in being a member of a group with the moral support that such teamwork affords, to say nothing of better hours of work and financial stability. Groups giving complete service, of course, must be composed of such proportions of generalists, who will be the patient's personal physicians, and specialists of appropriate sorts to supply at least all the usual special skills that comprehensive medical care requires.

As between generalist and specialist it can be said that the former has a richer experience in human relations; he knows and understands his patients better as persons, whereas the latter perhaps has greater intellectual satisfaction in gaining mastery of special technics and achieving scholarship in a defined field.

Choice of location—urban, suburban or rural—is governed by individual tastes. The majority nowadays flock to the cities. There is great need, however, for doctors in the less thickly settled areas. A few rugged extroverts accept the challenge of rural solo practice, but not in sufficient numbers adequately to solve the problem of rural medical care. It takes organization of well planned programs by community effort to do that. A number of such enterprises are already launched in various parts of the country. They are bound to increase in number and scope, and undoubtedly will be offering to many younger physicians and surgeons new and interesting opportunities.

Academic Opportunities

Full-time academic opportunities for doctors of medicine, as compared with those in private practice, are relatively few, but they are of great importance from the point of view of medical progress; also, their numbers are increasing because of both the increasing complexity of medical education and the greatly expanding medical research program of the nation.

A small number of medical graduates may elect to forgo all thought of practice or of any sort of clinical work, and instead to spend their professional lives in one of the preclinical sciences such as anatomy, physiology, biochemistry, microbiology, immunology or pharmacology. For such careers the medical training is not wasted, but it is by no means imperative. There are distinguished professors of these subjects on faculties of medicine throughout the land who are not doctors of medicine. Pathology, on the other hand, is much more closely integrated with clinical practice, and those who elect careers in this field, although they may never have direct care of patients, need a medical training to interpret their findings correctly.

Academic positions in the clinical departments of medical schools and their affiliated teaching hospitals, on the other hand, require the longest and most thorough training at the house-staff level of any of the medical callings. Aspirants for such positions must work up through all the grades of residents in either medicine or surgery, and usually top them off with some years in clinical research before they finally get on the ladder of university advancement in these disciplines. To such people falls the major responsibility of determining and leading the course of medical education. They are concerned with the organization of teaching and are ever seeking to improve its character and quality. They have the duty of enriching the educational process by integrating it with the investigative. In the university medical center the three functions of medicine—practice, teaching and research—are thoroughly blended to the enhancement of each. The full-time clinical teachers are for the most part the guides, guardians and activators of this process. To the scholarly-minded young doctor there are here challenging opportunities. Great happiness can be had in such careers, but the financial rewards are less than those obtained in private practice.

A variation of this type of career is that of the full-time clinical investigator: the doctor who is not so concerned (if at all) with teaching as those just described but who elects to spend his time entirely in the investigation of disease, making use for this purpose of clinical cases. In contrast to the anatomist, physiologist or biochemist, who conducts his investigations entirely in the laboratory and at the experimental level, the clinical investigator must thoroughly know his medicine for the very reason that he makes use of patients in his studies and is responsible for their welfare. The opportunities for careers of this type are rapidly increasing both in the clinical departments of medical schools and in a variety of research institutes. The Government, in particular since the

last war, has inaugurated research programs in several of its departments. These all require increasing numbers of competent clinical investigators. Notable among these undertakings is the newly opened Clinical Center of the United States Public Health Service, a research hospital with 500-bed capacity at Bethesda, Maryland. A veritable army of investigators will be required to make full use of such a volume of clinical material. It remains to be seen whether the divorcement from the process of medical education that this arrangement entails will prove altogether desirable in the long run. I have some doubts of it. The cross fertilization of practice, education and research will be lacking.

Miscellaneous Fields

There are other important fields of endeavor open to the doctor of medicine. Public-health work is one of the most significant and rapidly expanding of these. Just as medicine, in its relation to the individual, connotes practice, teaching and research, all these functions are intrinsic to the public-health profession.

To enter the public-health field the doctor of medicine, on graduation, may enter a school of public health and spend a year for certification, or three years for the doctorate in public health. Then he will probably perform his professional work on salary from the federal Government, a state or local government, a university or occasionally an industrial organization. He will not get rich, but if he is interested in medicine from the sociologic as well as the biologic point of view, he may find a highly satisfying and stimulating occupation in the public-health field. Industrial, or, as it is now called, "environmental," medicine is also offering a continually widening field.

Lastly I should like to apply the term "medical statesman" to certain of the careers that may more gradually open themselves to doctors of medicine. As governments and communities become more and more concerned with medical affairs, skilled leadership by medically trained persons will become increasingly important. The term "medical statesmen" (in contrast perhaps to medical politician) conveys, I believe, the meaning I have in mind without further elaboration. Such people are needed for the high medical positions of government, as deans to medical schools, as directors of great medical centers, as editors of medical journals, in industry and as leaders of health plans.

The decision to follow such a path will probably not be made early, but if the physician is broadly educated in the first place and has the capacity for leadership, he may, in mid-career or earlier, find himself emerging into some such activity. It is to the best interest of the people that some of the ablest doctors of medicine be recruited into the field of medical statesmanship.

Conclusions

Such, then, is briefly the general nature of the spectrum of professional opportunity offering itself to the young doctor of medicine. In making his choice of career he must look beyond the present and identify as clearly as possible the trend of development in medical affairs. I have tried to indicate some of these —for example, the changing nature and growing importance of psychiatry, the need for better organization for the provision of medical care, better co-ordination of the services of generalists and specialists, better integration of teaching, research and practice and the development of leaders who will help all these things come to pass.

MEDICAL PROGRESS

CURRENT CONCEPTS IN DIGITALIS THERAPY*

BERNARD LOWN, M.D.,† AND SAMUEL A. LEVINE, M.D.‡

BOSTON

THE use of digitalis marks the beginning of the modern era of cardiac therapy. Whole-leaf digitalis and the purified derivatives, the cardiac glycosides, continue as the most effective medicinal agents in the management of patients with congestive heart failure. The loss of cardiac reserve manifested by failure is the result of an imbalance between cardiac muscle strength and the work load imposed on the heart. Therapy is therefore directed toward improving the function of the failing heart muscle and reducing the work load on the myocardium. The two are intertwined; affecting one influences the other. Since the ultimate event in the chain leading to clinical failure occurs within the heart, the main therapeutic goal is to improve the vital function of the heart in propelling blood. The digitalis drugs are the only agents known to restore compensation through such direct action on the myocardium. All other measures are ancillary. The need for these supplementary measures in a given case varies inversely with the efficacy of digitalis.

During the last decade intensive study of the pathogenesis of one of the features of congestive heart failure — namely, edema accumulation — has focused attention on the kidney. A glomerular tubular imbalance has been suggested as the critical factor in the formation of cardiac edema.[1,2] Emphasis on the role of the kidney in increasing the cardiac load through salt and water retention has brought about a deviation from the concept of the primacy of the heart in initiating and sustaining failure. A stage has been reached at which arguments are being advanced to reassign to the heart the major role in the complex drama of congestive heart failure. The tendency to regard failure as the consequence of renal impairment has had therapeutic implications. As a result therapy is sometimes based exclusively on salt manipulation achieved through various regimens of dietary salt restriction, interference with intestinal sodium absorption and the promotion of renal salt loss. The mercurial diuretic and the weighing scale have been proposed as the vital implements for managing congestive heart failure.[3]

*From the Medical Clinic, Peter Bent Brigham Hospital, and the Department of Medicine, Harvard Medical School.
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†Formerly, assistant in medicine, Peter Bent Brigham Hospital.
‡Clinical professor of medicine, Harvard Medical School; physician, Peter Bent Brigham Hospital.

Recognition of the inseparable interaction of cardiac and extracardiac factors in the pathogenesis of failure must guide therapy. Translated into practice this means that digitalis is useful, with but few exceptions, during the entire course of the evolution of cardiac failure. In the early stages major reliance is placed on digitalis. Measures that diminish heart work, however, are not neglected. As decompensation advances and digitalis no longer overcomes the deterioration in cardiac competence, emphasis shifts to the restriction of salt intake and the promotion of salt loss. In the initial phases of decompensation the aim of therapy is to improve the function of the heart for the requirements of normal life. In the later phases the goal is to diminish the heart's burden and to bring it within the domain of limited cardiac performance.

As in Withering's day, the proper use of digitalis presents many problems. Questions of when and how to administer the drug as well as how to determine the adequacy of maintenance dosage are not yet fully answered. During the past three years new data on the action of digitalis have been acquired in this laboratory. In this report some of our work and the relevant studies of others are reviewed. These are considered from five points of view: the mode of action of digitalis and the clinical indications for its use; the toxic properties common to all therapeutically active digitalis-like preparations; the changes in the toxic threshold after alterations in body electrolytes; atrial arrhythmias frequently resulting from overdosage; and a method for predicting digitalis requirement for maximum therapeutic effect before digitalization.

ACTION OF DIGITALIS IN HEART FAILURE

Extracardiac Effects

The rational use of digitalis requires an understanding of its action on human cardiovascular dynamics. The effectiveness of digitalis in heart failure has been attributed to direct cardiac as well as extracardiac actions. Withering was impressed with the diuretic properties of digitalis and attributed improvement to drug action on the kidneys.[4] His contemporary, John Ferriar, was the first to conclude that the essential quality of the plant was exerted on the heart. Present-day concept is in accord with Ferriar's[5] view and holds that mobilization of edema is secondary to improved cardiac function.

Recent studies with Digoxin, however, show that this glycoside has a moderate but definite diuretic action.[6] In patients without edema or with noncardiac edema a slight increase in salt and water excretion follows its administration. When normal persons are given desoxycorticosterone acetate (DOCA) and an increased salt intake until edema forms, Digoxin induces a profound diuresis comparable qualitatively and quantitatively to that observed in congestive heart failure. In none of these subjects did digitalization produce alterations in renal or cardiac hemodynamics. Digoxin may therefore exert a direct effect on the renal tubules. Presumably, the drug depresses sodium reabsorption by competition with a DOCA-like adrenal steroid that it resembles in chemical configuration.[6] However, the improvement that occurs with digitalization in ordinary clinical failure frequently precedes and at times is not associated with any significant diuresis. This suggests that if a direct renal factor is operative it is in all likelihood subsidiary to the effect of digitalis on the cardiovascular system.

Is the clinical value of digitalis derived from a peripheral or central action on the cardiovascular apparatus? The reduction in venous pressure and the enhanced cardiac output after digitalization resemble the changes produced by tourniquet application or phlebotomy. McMichael and Sharpey-Schafer[7] therefore concluded that digitalis acts through venoconstriction. They reasoned that, by augmenting peripheral venomotor tone, digitalis lowered venous pressure, decreased venous return and lessened the overload on the heart. The result was a more efficient contraction and more complete emptying of the heart.

When ouabain was the glycoside tested the same observers found that in half the cases of heart failure there was a definite increase in cardiac output without associated changes in venous pressure. This indicated direct stimulation of the heart.[8] Others utilizing cardiac-catheterization technics found no relation between the magnitude of fall in venous pressure and the degree of increase in cardiac output. Furthermore, the increased cardiac output preceded the fall in the central venous pressure.[9] Similar studies in patients with isolated failure of the left ventricle demonstrated that with digitalization there was a significant increase in cardiac output and stroke volume accompanied by a decrease in pulmonary arterial pressure. These were achieved without alterations in right-ventricle end-diastolic pressure and could not be ascribed to the action of the drug on systemic venous pressure.[10]

Cardiac Action

Effect on the heart rate. In general there are two concepts of the mode of digitalis action on the heart. One school considers that restoration of compensation is an indirect effect mediated through reduction in rate, and the other attributes it to direct action upon the myocardium. Mackenzie[11] and Lewis[12] ascribed the benefits to depression of atrioventricular conduction and vagal slowing of the heart rate. Digitalis was therefore restricted to patients with atrial fibrillation and a rapid ventricular response. The larger number of patients whose failure was accompanied by regular rhythm frequently were not treated with digitalis. Such a view is no longer tenable. Extensive clinical data attest to the fact that patients with normal sinus mechanism are strikingly benefited. Experience with cardiac catheterization in failure demonstrates similar hemodynamic changes after digitalis irrespective of the underlying rhythm. It is now generally believed that, with the exception of certain atrial arrhythmias, slowing of the heart rate is the result of restored compensation rather than the converse. In patients with sinus rhythm digitalis may improve the clinical state before a material reduction of the heart rate. Therapeutic doses slow a rapid heart only in the presence of failure. When increased rate occurs without decompensation, as in the sinus tachycardias of fever anemia and thyrotoxicosis, digitalis is notoriously ineffective.

Atrial fibrillation may be an exception when rate reduction per se is a significant factor contributing to improvement. In patients with atrial fibrillation, who are highly susceptible to rate fluctuations, the ventricular rate reflects the state of compensation. When failure is accompanied by fibrillation with a rapid ventricular response, slowing invariably occurs with restored compensation. That rate reduction alone is a significant factor is indicated by the following observation. Occasionally, a patient with mitral stenosis and congestion, having normal sinus rhythm, fails to improve on digitalis only to show a distinct clinical improvement with the onset of atrial fibrillation. This change for the better may take place on the same dose of digitalis if the ventricular rate after the onset of fibrillation becomes slower than it was with sinus rhythm. This apparently results from the ability of the drug in this instance to slow the ventricles when the atria are fibrillating, in contrast to its failure to do so when the rhythm is regular.

Two mechanisms are operative in slowing the heart.[13] When small doses of digitalis are administered slowing is mediated by the vagus nerve and may be abolished by atropine or exercise. As the dose is increased, extravagal factors predominate. The resting rate with small or large doses of digitalis may be the same. When the slowing is merely vagal, however, physical exertion causes exaggerated acceleration of the heart.[14] These facts account for the observation that further improvement may be achieved after more digitalis without rate alteration. In patients with atrial fibrillation rate response to exercise serves as an effective gauge to the adequacy of therapy. Such a clear-cut indicator is absent in patients with normal sinus rhythm. This is in part responsible for the belief that digitalis is effective only in patients with atrial fibrillation.

Myocardial Action

The major pharmacologic effect of digitalis is its direct action on the myocardium. Digitalis increases the force of systolic contraction of heart muscle,[15] without alteration in the diastolic fiber size. The more forceful contraction results in more complete ventricular emptying with a rise in volume output. There is also an enhanced capacity to propel blood against increased peripheral resistance.[16] At the same time the duration of systole is abbreviated, allowing greater time for both ventricular filling and heart rest.[17] The diastolic size of the heart is reduced.[18] Since oxygen consumption is a function of the initial diastolic fiber length[19] such a reduction in size diminishes the oxygen expenditure for any work output.[20] The work capacity of the heart is increased, and a greater percentage of the liberated energy, therefore, is used in the mechanical processes of shortening and development of tension. The over-all result is an increase in cardiac efficiency and output. The basic pattern of myocardial derangement that characterizes failure is thus reversed. In other words the digitalized heart can do the same work with less energy (oxygen utilization) or more work with the same energy expenditure than before digitalization.

Clinical Use

The cardinal therapeutic value of digitalis in failure is its ability to increase a deficient cardiac output. In the usual case of chronic congestive heart failure the effect on the inadequate output is continuous. In the patient with incipient failure, increase in output may occur only during brief periods of the day when demands for volume or pressure work are beyond the capacity of the myocardium. Measurable increase in the cardiac output is not an invariable end result of digitalis therapy. It occurs only in the presence of congestive heart failure.

Harrison and Leonard[21] found that, when digitalis is given to normal dogs, cardiac output is decreased by about 25 per cent. Similar reductions were observed in human and animal studies in the absence of organic heart disease. In the presence of heart disease, as manifested by cardiac enlargement, but in the absence of failure, digitalis is also ineffective in raising the output. In a third of such patients studied at rest with cardiomegaly due to cor pulmonale and hypertensive, coronary or valvular disease, digitalis decreased the cardiac output. In the remaining patients of this group output was unchanged. These results with digitalis could not be related to a previous history of congestive heart failure, to heart size or to the initial level of the cardiac output.[22] The effect of digitalis in increasing cardiac output therefore depends on the qualitative alterations in cardiac metabolism associated with failure.

Although failure is a prerequisite for the myocardial effect of digitalis, its presence does not assure therapeutic effectiveness. The underlying process causing the failure is the critical determinant. Digitalis has little if any value when the disability is due merely to a mechanical constriction within the heart, as in some cases of tight mitral stenosis with pulmonary congestion and normal sinus rhythm. Digitalis provides no relief when the congestion derives from "pericardial embarrassment of the ventricles" interfering with ventricular filling such as that occurring in cardiac tamponade or constrictive pericarditis, unless concurrent myocardial failure exists.[23] Digitalis provides little benefit in the presence of active rheumatic carditis.[24,25] It also has limited value in cyanotic congenital heart disease.[26] Finally, digitalis affords no improvement in the majority of cases of so-called high-output failure.[27] This group is characterized by decreased peripheral arteriolar resistance. Although the resting cardiac output is elevated it does not suffice for body needs altered by metabolic or mechanical factors. It comprises such conditions as thyrotoxicosis, anemia, beriberi, osteitis deformans and arteriovenous fistulas.

In the majority of cases of heart failure the loss of cardiac reserve is associated with a decreased cardiac output. It is in this group of so-called low-output failure that the cardiac glycosides strengthen the contractile powers of the myocardium. Complete or partial resolution of failure generally occurs whether the etiologic factor is hypertensive, coronary, arteriosclerotic or valvular disease and is independent of the heart rate or the underlying atrial rhythm. Why digitalis is effective in failure and the manner in which the derangement is improved remain unsolved.

Physiochemical Basis for Digitalis Action

Suggestions regarding the biochemical site of digitalis action are being adduced from studies on the contractile elements of muscle. According to the stimulating ideas of Szent–Györgyi,[28] the contractile system of muscle consists of an elongated protein conjugate, myosin, and its precipitin, polymerized actin. These two proteins are attracted by colloidal forces, but are kept apart by an atmosphere of potassium ions. The excitatory impulse depolarizes the cell membrane, which thereupon becomes permeable to cations. This permits egress of potassium ions, and diffusion follows along the gradient of their ionic concentration. The loss of cellular potassium promotes the union of the contractile proteins. These proteins adsorb adenosinetriphosphate (ATP). The resulting actomyosin-ATP complex becomes maximally discharged and folded, with a loss of energy. The enzymatic hydrolysis of ATP follows, with myosin acting as an ATP-ase and with a release of its phosphate-bond energy to recharge the contractile system and return it to a relaxed state. During the recovery

phase of the cardiac cycle, catabolic processes reinvest energy into the ATP molecule so that it may serve again as the primary high-energy phosphate donor in the cell.

The complex process here outlined has been arbitrarily divided into two phases, one of energy production, during which substrate and oxygen are utilized, and another in which the available energy is converted into mechanical work.[29,30] In low-output failure Bing[30a] has shown that left ventricular blood flow per 100 gm. of myocardium is normal. A normal pattern of aerobic oxidation continues. The glucose oxygen extraction ratio rises from a normal range of 60 to 80 per cent to an average of 100 per cent, whereas the consumption of such substrates as lactate and pyruvate remains unchanged. Furthermore, the supply of ATP is undiminished. Thus, the biochemical lesion in low-output failure appears to be lodged not in the phase of aerobic energy release but rather in the conversion of the normally available energy into useful work.[29,30] Presumably, the defect resides in the overstretched contractile elements of the muscular machine.

On the basis of clinical experience that digitalis acts mainly in low-output failure the biochemical site of its action is apparently limited to the energy-utilization phase. It may therefore be anticipated that digitalis in some manner affects either the contractile elements themselves or the concentration of intracellular potassium that mediates the contractile action.

In vitro studies are providing evidence of such action. Digitalis can accelerate the spiraling of myosin threads.[31] Digitalis compounds also speed the polymerization of actin, a stage preliminary to its union with myosin. This is true only of cardiac actin, but not of actin derived from skeletal muscle.[32] Friedman and St. George[33] studied the intracellular fate of digitoxin in heart muscle and liver by means of ultracentrifugation and assay of the fractions for their digitoxin content, utilizing the duck-heart preparation. Digitoxin was not found in the mitrochondrial components where enzymes concerned with the glycolytic process of the Krebs cycle are situated but was abundantly concentrated in the area of the cell containing ATP, actin and myosin. This is in accord with the view that digitalis acts on the contractile elements of the cardiac cell. Digitalis, furthermore, affects cellular potassium concentration. Therapeutic doses are said to increase, and toxic doses to decrease, cellular potassium content.[34-36] These studies are unfolding the basis for the specificity of digitalis action in low-output failure.

Other Uses

Whereas the prime value of digitalis is derived from its therapeutic action on the myocardium, certain other properties find clinical use. In large doses digitalis impairs conduction in the atrioventricular junctional tissue and also prolongs the conduction recovery time of atrial muscle. These actions are utilized in atrial flutter and fibrillation. When these arrhythmias are being converted by quinidine, the atrial rate diminishes; this, together with the atropine-like effect of quinidine on the vagus is conducive to increased facility of atrioventricular conduction with accelerated ventricular response. The increased heart rate may necessitate interruption of quinidine therapy. In such cases large doses of digitalis, by delaying atrioventricular conduction, may prevent bouts of tachycardia. In some cases of atrial flutter digitalis is directly effective in converting the arrhythmia to a more easily managed fibrillation. In addition it is the agent of choice in the treatment of paroxysmal atrial tachycardia when simpler measures of vagal stimulation have proved unavailing.

Additional Clinical Comments

As an illustration of the application of some of the principles discussed, one might comment on a frequent error that prevails in general practice. Many patients in the latter decades of life who complain of dyspnea are not helped by digitalis. The drug is given because heart disease is the usual cause of shortness of breath in the elderly person. In these cases, however, the dyspnea proves to be bronchial in origin and part of the picture of pulmonary emphysema. This error could readily have been avoided because the heart under these circumstances not only is not enlarged but also may even be smaller than normal. From the previous physiologic considerations it could be inferred that if the heart is not dilated, it is very unlikely that digitalis would afford any benefit.

There are conditions in which certain signs and symptoms simulate heart failure but digitalis is worthless. Patients may have dyspnea, rales and varied pulmonary findings owing to bronchiectasis, lung tumor or other primary respiratory disease — manifestations that are common in heart failure and yet occur without heart disease. Similarly, an enlarged liver due to Laënnec's cirrhosis or neoplasm may be confused with right-sided failure. Finally, peripheral edema has numerous causes apart from heart failure. In all these cases simple hemodynamic studies, such as determinations of venous pressure and circulation time, as well as x-ray examination for vascular congestion of the lungs, may serve to establish the presence of heart failure.

A converse example in which symptoms are lacking and yet digitalis proves of value is in the patient with hypertension who exhibits a diastolic gallop. Such a patient may not experience significant breathlessness or paroxysmal nocturnal dyspnea though the heart muscle is already in the early stages of failure that digitalis may remedy.

The varying actions of the digitalis drugs do not require different preparations. To date no fundamental differences have been found among the digitalis glycosides in their effect on the heart. The dis-

similarities encountered are quantitative and related to the rapidity and degree of absorption and variability in potency and duration of action. Nevertheless, the continuing release of new digitalis preparations with claims of special efficacies causes many a physician to engage in a will-o'-the-wisp pursuit after the ideal agent. The result is that he does not master the use of a single one. The conclusion is that adequate experience with one purified digitalis glycoside in addition to digitalis leaf permits one to cope with nearly all clinical situations in which digitalis is indicated.

Digitalis Intoxication

Subjective Manifestations

Although idiosyncrasy or hypersensitivity rarely if ever occurs, digitalis toxicity has been a problem since the introduction of this drug. Little can be added to the keen observation of Withering[4] on the results of overdosage:

> The foxglove when given in very large and quickly repeated doses occasions sickness, vomiting, purging, giddiness, confused vision, objects appearing green or yellow, increased secretion of urine with frequent motions to part with it and sometimes inability to retain it; slow pulse even as slow as 35 in a minute, cold sweats, convulsions, syncope and death.

All therapeutically active digitalis preparations may produce toxicity. The absence of toxic properties in a digitalis body is evidence of the cardiotonic inertness of the preparation.[27] The occurrence of toxicity bears no relation to the digitalis compound employed but is conditioned by the extent of failure, the underlying etiology of the failure, the cardiac reserve, the electrolyte balance, the concurrent use of other drugs and numerous other factors.

Anorexia, nausea and vomiting are among the earliest and most common subjective manifestations of digitalis overdosage. These symptoms occur whether the drug is administered orally or intravenously.[37] Emetic movements are not prevented by the extirpation of the gastrointestinal tract or by extensive afferent denervation of visceral structures. The vomiting is thus of central rather than peripheral origin. These symptoms may be obscured by concomitant gastrointestinal disease and may be indistinguishable from similar symptoms arising from liver and bowel congestion. Advanced intoxication as evidenced by objective data sometimes occurs in the absence of all subjective indications of overdosage.[38]

About 25 per cent of patients with digitalis intoxication experience either visual symptoms or dizziness. The dizziness is a true vertigo and may make the ambulatory cardiac patient bed ridden. The visual disturbances are characterized by blurring, dancing or flickering dots before the eyes and color aberrations.[39] These symptoms are trivial in comparison with the gravity of the underlying disorder. Information about the presence of ocular symptoms is often not volunteered and is elicited only after careful questioning.

Headache is a fairly common finding and may be the sole symptom preceding disturbances in cardiac rhythm. Unusual neurologic symptoms have been observed in about 9 per cent of patients suffering from digitalis intoxication. These consist of pains in the lower third of the face resembling trigeminal neuralgia associated with typical neuralgic shooting pains in the upper extremities, lower lumbar areas and calves. In patients receiving large intravenous doses of the strophanthin derivative, acetyl strophanthidin, numbness and tingling of the lips, tip of nose, cheeks and ears are frequently noted. In the elderly and those with advanced congestive heart failure central-nervous-system findings may predominate, with lassitude, apathy, confusion, disorientation, delirium, stupor, aphasia and at times psychotic behavior patterns. Degenerative glial and ganglionic cellular changes in the brain stem and cerebellum have been found in laboratory animals poisoned with digitalis.[40]

Cardiac Disturbances

The most important toxic effect of digitalis is on the heart. Every form of arrhythmia and conduction disturbance has been attributed to this drug.[41] In the presence of severe myocardial damage it is a common cause of ventricular tachycardia.[42] Next to coronary-artery disease it is probably the most important precipitant of advanced heart block.[43] These extreme reactions define the toxic potential of digitalis both as a myocardial irritant and as a depressant. The interaction of these two effects make possible the observed gamut of electrocardiographic anomalies.

Irritative phenomena resulting in ectopic rhythms have been regarded as predominantly restricted to the ventricles. Recent studies demonstrate the frequency and specific form of similar arrhythmias in the atria.[44] This group of atrial arrhythmias and some other toxic manifestations on the heart are dealt with below in a subsequent section.

The depressant action of digitalis is mainly limited to the atrioventricular junctional tissue where the direct and indirect (vagal) actions of digitalis are synergistic. Sinoatrial and intra-atrial block and standstill of the atrium are rare. This is explained by the antagonism between the vagus nerve and direct digitalis effects on conduction recovery time in the atria.[45] Bundle-branch block and intraventricular conduction impairment are unusual sequelae of overdosage, possibly owing to the absence of vagal influence on the ventricular myocardium.

The earliest electrocardiographic evidence of digitalization consists of shortening of the QT interval, ST-segment scooping and inversion of the first portion of the T wave. These changes provide no index of the therapeutic adequacy of the drug, nor do they permit prediction of the proximity or even the presence of toxicity. Severe digitalis poisoning frequently occurs in their absence.[46]

In man, except for the gastrointestinal symptoms, ventricular extrasystoles are the most common indications of overdosage. When digitalis is continued in their presence the ectopic beats assume the fixed pattern of bigeminy or coupling. The occurrence of bigeminal rhythm without digitalis overindulgence generally indicates serious, frequently terminal, heart disease. According to McMichael[47] the final stage of myocardial breakdown has been reached when digitalis ceases to be of benefit: "In its presence it is never wise to give digitalis." This statement is valid if restricted to patients in whom bigeminy has been clearly induced by digitalis. In those in whom bigeminy develops without medication adequate digitalization may abolish the arrhythmia. In such cases the ventricular premature beats are expressions of congestive heart failure, inadequate coronary perfusion and myocardial anoxia, with a consequent increase in ventricular irritability. Distinction between the two types of bigeminy is important. In one group continued use of digitalis may produce fatal arrhythmias, and in the other it may afford some benefit.

Sagall and Wolff[48] have defined the characteristics of the bigeminal rhythm resulting from an overdose of digitalis. In the digitalis group the etiology of the heart disease is most frequently rheumatic, and the underlying rhythm is atrial fibrillation. The ectopic beats tend to be initiated in the right ventricle. When these factors are associated with multifocal extrasystoles, digitalis is almost invariably the causal factor.

The duration of digitalis bigeminy ranges from a fleeting occurrence to a continuous bout lasting for as long as thirty-four days.[49] The persistence of this rhythm is a function of the severity of the heart disease and the type of digitalis used. The longest durations are encountered with digitoxin, and the shortest episodes follow ouabain and other strophanthin derivatives.

The continued administration of digitalis in the presence of bigeminy may cause the emergence of a prodromal phase of ventricular fibrillation.[50] This prefibrillatory state is characterized by the increasing frequency of ventricular premature beats, polymorphism of abnormal and normal beats, salvos of multifocal premature beats followed by unidirectional or bidirectional ventricular tachycardia. The penultimate danger of digitalis poisoning is ventricular fibrillation. In patients with advanced heart disease the prefibrillatory state and death may be caused by small amounts of this drug. Death from digitalis may also occur on maintenance therapy after profuse diuresis.[51,52]

Other Toxic Effects

Generalized muscular weakness has been noted as a reaction to an overdose of digitalis.[53] Prolonged digitalis maintenance has been implicated in gynecomastia occurring in elderly men with congestive heart failure.[54] The enlargement of the breasts develops after the restoration of compensation when liver-function studies exhibit but minimal derangement. Since the digitalis glycosides structurally resemble the gonadal steroids an estrogenic effect has been postulated.

It has been claimed that digitalis promotes intravascular thrombosis by shortening the coagulation time and increasing heparin tolerance. Other investigators have been unable to confirm these findings. Askey and Neurath[55] observed that digitalization of patients with atrial fibrillation and myocardial infarction enhanced the mortality. Death was due to embolization of the greater circulation. Similar thrombotic tendencies have been noted after diuresis produced by mercurial agents and have been attributed to hemoconcentration and increased blood viscosity. Perhaps, as suggested by Pere,[56] any effect that digitalis has on the clotting mechanism is due to its promotion of diuresis.

Gravity of Digitalis Intoxication

In the nonfibrillating patient, in whom a clear-cut endpoint for digitalization is at times lacking, it is customary to digitalize to mild toxicity to assure full therapeutic action. There is thus but a narrow boundary between the two areas. Digitalis therapy hovers in the shadow of intoxication for still another reason. The margin of safety with all preparations is limited. For any digitalis agent approximately 60 per cent of the toxic dose is required to achieve a therapeutic effect. In this respect Digoxin, digitoxin and lanatoside C offer no advantage over digitalis leaf.[57-59] An exception may be gitalin, a water-soluble amorphous mixture of glycosides extractable from *Digitalis purpurea*. Batterman and his co-workers[59,60] claim that with gitalin only a third of the toxic dose is required for the therapeutic effect. This finding awaits confirmation. With all digitalis compounds, once toxicity emerges, a substantial percentage of the fatal dose has been administered. When ventricular extrasystoles are produced in animals, from 50 to 80 per cent of the minimal lethal dose has been given.[61,62]

Electrocardiographic evidence of overdosage is not always present. Advanced intoxication may exist continuously with only sporadic electrocardiographic manifestation. Bigeminy in such cases can be brought on by slight exertion, deprivation of oxygen therapy, straining on the bed pan or emotional upset. The electrocardiogram at one moment shows a perfectly normal rhythm whereas a few minutes later ventricular tachycardia may dominate the picture. With advancing congestive heart failure the margin between therapeutic and toxic effects decreases. In such patients, in the absence of telltale ventricular premature beats to arouse suspicion of overdosage, a mercurial diuresis may be fatal.

Toxicity can be of prolonged duration even after the discontinuation of digitalis. When nausea, vomiting and extrasystoles appear the practice is to stop

digitalis. If the symptoms persist unaltered after three or four days or more the difficulties are attributed to the severe failure rather than to the digitalis. The resumption of digitalis under these circumstances is hazardous and further compromises a limited cardiac reserve. When critical electrolyte shifts are effected in animals digitalis toxicity usually persists for the duration of the electrolyte derangement. By this means toxicity has been prolonged forty times its usual duration.[63] If the same phenomenon held true for the human being in cardiac failure, who also suffers grave disturbances in electrolyte pattern, toxicity would last many months after digitalis had been stopped. This may account for the observation that small amounts of digitalis can initiate grave arrhythmias even after the patient has been without digitalis for some months.

The frequency and gravity of digitalis intoxication is not widely appreciated. This is due in part to a lack of well defined myocardial lesions resulting from toxic doses. In animals an excess of digitalis produces areas of necrosis and fibrosis, especially in the subendocardial regions of the left ventricle.[64-66] The administration of atropine diminishes and that of epinephrine increases the susceptibility of the tested animals to the pathologic lesions. The underlying mechanism for the necrosis may be severe coronary vasoconstriction or a shortened period of coronary filling.[67] No morphologic changes have been noted in man. Since death from digitalis finds no pathological corroboration the significance of the digitalis toxicity is often overlooked. The exceptions are the rare cases with continuous electrocardiographic tracings taken just before death. There are only 6 cases of digitalis-induced ventricular fibrillation reported in the literature with electrocardiographic substantiation.[50]

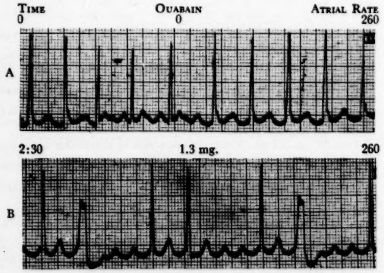

FIGURE 1. *Electrocardiograms in a Twenty-Year-Old Man without Organic Heart Disease but with a Spontaneous Episode of Flutter.*

A shows the tracing on maintenance digitalis therapy, and B the tracing after 1.3 mg. of ouabain had been given intravenously to induce further ventricular slowing. Occasional premature ventricular beats occur over a period of nine minutes.

Differences in Myocardial Reaction to Digitalis

In patients without heart disease ventricular premature beats or bigeminal rhythm seldom results from digitalis overdosage. Sagal and Wolff[48] gave digitalis to 100 normal persons. They observed ST-segment deviations and T-wave and PR-interval changes, but only two ventricular premature beats were recorded in 300 electrocardiograms. According to McMichael,[47] digitalis bigeminy is not seen in the intact mammalian heart in situ. In the New York insurance fraud cases of the thirties large amounts of digitalis were ingested in the attempt to simulate heart disease; only occasional extrasystoles were detected in this group. Bigeminal rhythm was not noted.[68] Such rhythms have not been observed in persons taking large doses accidentally or with suicidal intent. Apparently, myocardial injury is essential for the rhythm derangement of the ventricle induced by toxic quantities of digitalis.

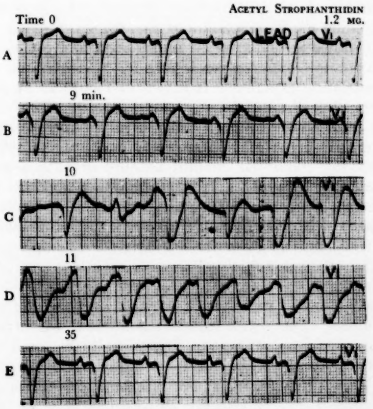

FIGURE 2. *Electrocardiograms in a Fifty-Six-Year-Old Man with Severe Right-Sided and Left-Sided Failure Who Had Received No Digitalis for Five Months.*

Acetyl strophanthidin, 1.2 mg., was given intravenously (A). This was followed within five minutes by ventricular premature beats (B) and in nine minutes by anomalous atrioventricular conduction, or Wolff–Parkinson–White syndrome (C). Aberration of the ventricular complex (D) and intraventricular block and flutter then occurred. Thirty-five minutes after the digitalis administration a normal sinus mechanism was restored (E).

Two patients provide striking illustration of this point. In 1 of these whose electrocardiogram is shown in Figure 1, a prolonged episode of atrial flutter developed spontaneously. To reduce the rapid ventricular rate he was given 2.5 gm. of digitalis leaf in the course of a few days. The rate remained unaffected, and he was maintained thereafter on 0.2 gm. of digitalis leaf daily. In a further effort to slow the ventricles before quinidine therapy, 1.3 mg. of ouabain was administered intravenously over a period of two and a half hours. Atrioventricular block was enhanced, and the ventricles were slowed. Notwithstanding the large amount of digitalis, he experienced no subjective evidence of intoxication and exhibited only a few extrasystoles lasting for nine minutes. A contrasting experience is shown in Figure 2. A patient with severe right-sided and left-sided failure due to coronary-artery disease and previous anterior and posterior myocardial infarctions* had been off digitalis for about five months because of nausea and vomiting. To test his responsiveness to digitalis, he was given 1.2 mg. of acetyl strophanthidin intravenously — equivalent to a dose of 0.6 mg. of ouabain. Within five minutes he exhibited ventricular premature beats. A bout of "anomalous atrioventricular conduction" (Wolff–Parkinson–White syndrome) followed. Shortly thereafter, a prefibrillatory rhythm developed. The severe intoxication lasted for about thirty minutes. Two days later half the dose of acetyl strophanthidin again evoked marked toxicity.

These 2 patients demonstrate both the difficulty and the ease of producing intoxication. The underlying status of the myocardium is one of the important factors responsible for this difference. The normal, therefore, differs from the failing heart both in response to beneficial and in toxic actions of digitalis. It may be that toxicity is but an extension of the therapeutic effects at the cellular level.

*This case is more fully discussed by Enselberg et al.[50]

(To be continued)

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MEDICAL INTELLIGENCE

DOCTORS AFIELD

Moses Maimonides

SOLOMON E. BARR*

WASHINGTON, D.C.

ALTHOUGH Moses Maimonides was one of the most famous physicians of his day he was even better known as a philosopher, leader and scholar.

He was born in 1135 in Moslem-controlled Cordova, Spain, the eldest son of Maimon, a local judge. When Moses was thirteen a fanatic new Moslem sect, the Alhomades, conquered his native city. Because of the ensuing religious persecution he and his family were forced to flee to Morocco. However, conditions were no better there, and ten years later the family again fled, this time to Fostat, Egypt, a suburb of Cairo. There the family engaged in gem importing. After the death of their father his younger brother David took over the management of the family business so that Moses would be able to continue his medical and religious studies. However, tragedy struck when his brother David was lost in a shipwreck, together with all the family fortune, leaving Moses destitute and burdened with the support of his brother's widow and child. He then concentrated on his medical practice. His fame as a physician soon spread, and he was appointed personal physician to the court of Saladin, Sultan of Egypt.

At the age of thirty-three he completed his first great work, *The Luminary*. This book contains the "Thirteen Dogmas," which have since become recognized as one of the most popular definitions of orthodox Judaism. *The Luminary* also includes a section on ethics often studied separately and known as the "Eight Chapters." In 1172 he was elected head of the Cairo Jewish community. Neither this public position nor his other one as court physician to the Sultan carried any salary, but they took up a great deal of his time. Maimonides was obliged to walk to the Sultan's palace every morning, often not returning until late afternoon to attend to his busy medical practice.

Moses Maimonides (From Sculpture by Doris Appel).

Despite these handicaps he accomplished in the short space of ten years what no one before him had

*Fourth-year student, George Washington University School of Medicine.

ever been able to do: he wrote a complete commentary on the Talmud. This book, the *Mishneh-Torah,* consisted of 14 volumes and over 1000 chapters. It brought him instant fame but also many enemies who disagreed violently with some of his opinions. To clarify his beliefs he wrote the last of his three great works, *The Guide of the Perplexed.* Published during his fifty-fifth year, this book is an explanation of his philosophy addressed to his most brilliant pupil, Joseph ibn Aknin.

His last fifteen years were devoted to his duties as physician, leader and adviser to the Sultan. He died in 1204 and was buried in Palestine.

One of the characteristics of his philosophy was his ability to weld together supposedly antagonistic beliefs. He incorporated the pagan Greek and the Jewish-Christian-Moslem ideals into a unified system of ethics. To the Greeks the moral value was satisfied by a mean between deficiency and excess: beauty is truth, and truth harmony. But the Greeks lacked the nonpagan ideals of humility, charity and forgiveness. Maimonides pointed out that men must have a balance in their moral values — humility must not be groveling, nor charity weak, and forgiveness must at times give way to indignation. Unlike many philosophers of his time he was not bothered by the problem of faith versus reason. To him they were not antagonistic but synergistic.

Of even greater importance today is his concept of science and religion. To Moses Maimonides they were part of the same truth. He believed much of the Bible to be an allegory illustrating the eternal fight between good and evil. Where science conflicted with the literal translation of the Bible this simply meant that the Testament had to be reinterpreted, not that either religion or science had to be discarded.

In this manner he helped pave the way for many of the great philosophers who followed him. Some of his works were translated into Latin as early as the first half of the thirteenth century. In the works of Albert Magnus, the great Catholic thinker of the thirteenth century, there are numerous references to "Rabbi Moses the Egyptian." Thomas Aquinas also cites him frequently. Of all the great philosophers Spinoza was probably the most strongly influenced by Maimonides and took him as his guide. The complete works of Maimonides have now been translated into all the major languages of the world.

To Moses Maimonides medicine and religion were complementary to one another — one treating the body, and the other the soul. He was one of the great physicians of the Middle Ages and attracted patients from all corners of the earth. Richard the Lion-Hearted is said to have made him an offer to become his court physician. Unlike most of the other doctors of his day he rejected superstition and astrology, trying to base his therapy upon scientific ground. He emphasized sanitation, cleanliness and prevention of disease. In his book on psychiatry he revealed an almost modern concept of the influence of the mind on the body. He wrote many treatises on medicine, the most famous being *Poison and Its Cure,* which was concerned mainly with snake bites and their treatment. This treatise on poison was considered an authoritative source for hundreds of years.

Every morning before Maimonides started his day's work he repeated his "Prayer of a Physician." This prayer, parts of which are as follows, could well serve as an ideal guide to the physician of today:

. . . Grant that I may be filled with love
For my art and for my fellow-men.
May the thirst for gain and the desire for fame
Be far from my heart.
For these are the enemies of Pity
And the ministers of Hate.
Grant that I may be able to devote myself, body and soul,
To Thy children who suffer from pain.
Preserve my strength that I may be able to restore
The strength of the rich and the poor,
The good and the bad, the friend and the foe.
Let me see in the sufferer the man alone.
When wiser men teach me, let me be humble to learn.
For the mind of man is so puny
And the art of healing is so vast.
. . . Let me be intent upon one thing, O Father of Mercy —
To be always merciful to Thy suffering children.

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Correction: In the opening sentence of the second paragraph on page 622 of the Ingalls and Purshottam article, "Oxygenation and Retrolental Fibroplasia," which appeared in the April 15 issue of the *Journal,* the phrase "33 cases of RLF" should be changed to read "3 cases of RLF."

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

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CASE 40181

PRESENTATION OF CASE

First admission. A seventy-five-year-old childless widow was referred to the hospital because of weakness and giddiness.

Eight years previously she began having ankle swelling, exertional dyspnea, paroxysmal nocturnal dyspnea and occasional fleeting pains over the left side of the chest that radiated to the left shoulder. Eighteen months before admission she was admitted to another hospital because of pneumonia. At that time, because of "marked variation in size and shape of erythrocytes and an erythrocyte count of 1,000,000," "liver shots" were started. Six months before admission she was again admitted to another hospital because of extreme weakness, syncope and ankle edema and was given four blood transfusions. A diagnostic work-up, including barium-enema examination and gastrointestinal and gall-bladder series, was negative. One month before admission, because of weakness, giddiness on standing, orthopnea relieved by four pillows and ankle swelling, she was again admitted to the hospital and given three blood transfusions. The stools at this time were said to be normal. After discharge she felt generally well, but when severe dyspnea on the slightest exertion and orthopnea requiring four pillows for relief again developed she was referred to this hospital.

As a child the patient had been anemic, though she had allegedly been cured by eating raw bone marrow of freshly killed beef. There was no family history of anemia or Mediterranean-basin ancestry. She denied easy bleeding or easy bruising. In the past eighteen months she had noted on sporadic occasions that the stools were dark and often black. She attributed this to Agoral, which had been prescribed eighteen months previously for increasing constipation. She had always had a good appetite, and she denied any gastrointestinal symptoms but "gassiness" provoked by fatty foods. She did not know whether she had lost weight recently.

Physical examination revealed a very sallow woman in respiratory distress. At a semireclining position of 60° the neck veins were distended up to the mastoid process. The left border of the heart was at the midclavicular line, and the rhythm was regular. There was a Grade 2, shrill, high-pitched apical systolic murmur. The aortic second sound was of lower intensity than the pulmonic. There were medium crackling rales in the right side of the chest up to the angle of the scapula, and scattered rales in the left base. The liver edge was felt 10 cm. below the right costal arch. Rectal examination was negative; there was no ankle edema.

The temperature was 99°F., the pulse 86, and the respirations 22. The blood pressure was 140 systolic, 70 diastolic.

Urinalysis was negative. Examination of the blood demonstrated a hemoglobin of 2.5 gm. per 100 cc. and a white-cell count of 28,400, with 82 per cent neutrophils, 12 per cent lymphocytes and 6 per cent monocytes. The rell cells showed hypochromia, with moderate variation in size, but not in shape; occasional microcytes were present. The Coombs test was negative. The total protein was 5.6 gm. per 100 cc.; other blood chemical determinations were normal. The bromsulfalein test showed 3 per cent retention of the dye in thirty minutes. The cephalin flocculation was ++ in forty-eight hours. A blood culture was negative. The prothrombin time was 100 per cent. A stool gave a +++ guaiac reaction. An electrocardiogram showed a normal sinus rhythm at a rate of 110, probably old posterior myocardial infarction and prolonged intraventricular conduction. Roentgenograms of the chest disclosed an enlarged heart, with a cardiothoracic ratio of 16:26. The aorta was tortuous and calcified. The pulmonary vessels on both sides were engorged. There was some increased density in the right lower lobe. Barium-enema and barium-swallow examinations were negative. A bone-marrow aspiration revealed an erythroid hyperplasia and an adequate number of megakaryocytes.

In the first few hours after admission the patient was given oxygen and blood transfusions, with much improvement. During the first week in the hospital she received four transfusions of whole blood and packed red cells, and the hemoglobin rose to 10.7 gm. per 100 cc. The white-cell count fell to 9250; the reticulocytes were 2.3 per cent. After eighteen days in the hospital the stools were guaiac negative and she was discharged considerably improved. Ferrous sulfate and digitalis were prescribed.

Second admission (ten months later). In the interval she had been followed in the clinic and had been maintained on a cardiac regimen for congestive

heart failure. She was taken to the hospital because of weakness. She had not had a bowel movement for the past several days, and had taken milk of magnesia, after which she noted black, tarry stools tinged with red on the surface. On the day of admission she had three episodes of vomiting, and crampy abdominal pain. Physical examination was unchanged from that made ten months previously. The patient looked wan and weary.

The temperature was 99°F., the pulse 90 and the respirations 14.

The urine was normal. The hemoglobin was 8.0 gm. per 100 cc., and the white-cell count 12,800. The blood chemical determinations were within normal limits. A stool specimen gave a + + + + guaiac test. Aspiration of stomach contents was negative for blood. A Miller–Abbot tube was passed for a distance of 147 cm. before guaiac-positive material was aspirated. At 165 cm. the material aspirated gave a + guaiac test. Barium-enema and barium-swallow examinations were again negative.

During the hospital stay the patient continued to have occasional episodes of tarry stools. She refused operation and was discharged on the nineteenth hospital day after receiving eleven blood transfusions. The hemoglobin had been stable at 10 gm. per 100 cc. for forty-eight hours.

Third admission (twelve days later). Since discharge she had been able to do her own cooking and to be up and around the house. She was followed in the clinic, and when the hemoglobin was noted to be 4.9 gm. per 100 cc. she was again referred to the hospital. She claimed to feel well but she appeared pale and chronically ill. Physical examination showed no important change since the previous admission. The blood pressure was 120 systolic, 80 diastolic. The stool guaiac test was + + + +.

She was given seven blood transfusions, and the hemoglobin rose to 12.8 gm. per 100 cc. Clinically, there was no change. One of five subsequent stool guaiac tests was positive. On the tenth hospital day an operation was performed.

Differential Diagnosis

Dr. Daniel S. Ellis*: It seems to me that this patient had arteriosclerotic heart disease, probably exacerbated by a chronic anemia to the extent that she had been in and out of chronic congestive heart failure. I have no reason to doubt that diagnosis. The real problem is why she was anemic. Nothing in the protocol makes me believe that chronic blood loss through the gastrointestinal tract was not the cause of the anemia. The peripheral blood and bone-marrow studies were all consistent with chronic blood loss, and the fact that she repeatedly had guaiac-positive stools seems to confirm such an impression. The significance of the statement that when a child she had been anemic and been cured by eating bone marrow I shall discount because I doubt if that episode had any effect on the present illness. Therefore, this problem becomes one of differential diagnosis of the causes of blood loss from the gastrointestinal tract, where no lesion was demonstrated. Perhaps Dr. Hanelin will show us the x-ray films, which he has already told me will not help me. The protocol states that a barium-swallow examination was done; it does not indicate whether a full gastrointestinal series was included.

*Assistant physician, Massachusetts General Hospital.

Dr. Joseph Hanelin: Only at the first admission was a complete series done — that is, examination of the large bowel, upper gastrointestinal tract and small bowel. The chest films at that time show an enlarged heart, with predominant enlargement of the left ventricle, engorgement of the pulmonary vessels and what may be pulmonary edema or pneumonitis on the right side. There is no pleural effusion.

Dr. Ellis: Is that the increased density that was mentioned?

Dr. Hanelin: Yes; that is the only film that we have in the collection. For some reason no other films were made — at any rate we do not have them. I should have liked to see this density followed by further examinations.

Dr. Ellis: Do you think it is tumor?

Dr. Hanelin: It is probably not tumor. There is a suggestion in the films of the abdominal examination taken some months later, in which the right lower portion of the lung is included, that the density has cleared. The barium-enema examination was reported to be negative and is negative from what I can make out in the films. In the upper gastrointestinal tract, also, I see no gross lesions. There was a follow-up study of the small bowel at that time. From film evidence I cannot indicate any source of hemorrhage. On the last admission, nine months later, the only films I have are those of the stomach, which also do not help us.

Dr. Ellis: There is no evidence of a hiatus hernia?

Dr. Hanelin: No.

Dr. Ellis: Can you tell anything about the esophagus — whether or not there were varices?

Dr. Hanelin: I do not see any varices.

Dr. Ellis: Was there a gastric analysis?

Dr. Robert F. Moore: There was no gross or occult blood in the gastric contents. Acid was present.

Dr. Ellis: Was a cytologic examination done?

Dr. Moore: No.

Dr. Ellis: The liver edge was felt 10 cm. below the right costal arch. Was the liver hard or soft, smooth or nodular, and was its edge sharp or rounded?

Dr. Moore: It was smooth and not hard; the edge was rounded; it was tender on the first admission.

Dr. Ellis: Did it get smaller when the heart became better compensated?

Dr. Moore: Yes; it did.

Dr. Ellis: With the information given and the fact that the liver was not firm, hard or nodular

I can say that there was no evidence of metastatic disease in the liver; I should prefer to think that it was enlarged because of congestion.

The clues to the site from which this patient was bleeding are very meager. The stomach was aspirated, and the gastric contents were guaiac negative; then a tube was put into the small bowel to a distance of 147 cm. before guaiac-positive material was obtained; it was also present at 165 cm. She had tarry stools, which gave a ++++ guaiac reaction, with some red streaking on the side. The tarry stool is a further clue to bleeding from the upper gastrointestinal tract rather than from the colon. The x-ray examination of the gastrointestinal tract leaves something to be desired in completeness. No mention was made of sigmoidoscopic study. Also, on one occasion she had attacks of nausea and vomiting and crampy abdominal pain. Can anybody tell us in what part of the abdomen there was pain?

DR. MOORE: It began in the midabdomen and radiated down to the right lower quadrant almost to the femoral area.

DR. ELLIS: Did she have a femoral hernia? This type of pain is likely to be due to small-bowel disease.

DR. MOORE: No; she did not.

DR. ELLIS: She had, I think, chronic bleeding from the gastrointestinal tract, probably the small bowel. The causes of such bleeding are many. I have listed about ten, which I am going to mention. In a patient of this age without previous symptoms, a large hiatus hernia is often the cause of chronic blood loss. Esophageal varices may bleed for a long time and may present as unexplained anemia. Nothing supports a diagnosis of liver disease or portal hypertension, and no evidence of esophageal varices was mentioned. All gastrointestinal symptoms that might lead to a diagnosis of ulcer were either not elicited or not present. Moreover, I think it would be unusual for a woman of seventy-five years of age to bleed to this degree from a duodenal ulcer without having had a history or x-ray evidence of an ulcer. Likewise, there was nothing to suggest a chronic gastritis, which could do the same thing. Carcinoma is certainly a possibility, but there was no evidence of it in the stomach. The x-ray findings and the length of the history are against this diagnosis. It is conceivable that a lesion in the chest had metastasized to the small bowel and was causing the bleeding. I recall a case* discussed at one of these conferences not too long ago of a patient with a carcinoma of the lung and multiple small-bowel lesions that presented as intussusception and obstruction rather than bleeding, but I see no reason why any such nodule could not present as bleeding. I have no ground on which to make this diagnosis since Dr. Hanelin does not think there was a carcinoma. Ulcerative colitis, it seems to me, is ruled out by the barium-enema examination and by the fact that the stools were tarry and only intermittently guaiac positive. It seems unlikely that a woman of seventy-five would have a Meckel diverticulum causing this picture. Other very rare conditions are a cirsoid aneurysm of a gastric vessel, which I have no reason to believe was present, and a ruptured arteriosclerotic vessel not accompanied by peptic ulceration, which might have been chronically bleeding.

That brings me to the intramural tumors of the small bowel — the leiomyomas or leiomyosarcomas, which may ulcerate. These intramural tumors may elevate the mucosa sufficiently to appear polypoid. Perhaps the episode of crampy pain, with nausea and vomiting, was related to some mechanical disturbance in the small bowel resulting from a polypoid or intramural lesion. I shall say that she had a polypoid lesion, either an adenomatous polyp or a leiomyoma, more probably the latter, of the small intestine that had caused chronic blood loss. The long history seems to rule out a carcinoma of the small bowel.

DR. EDWARD F. BLAND: I should like to say that for a woman of seventy-five to maintain a blood pressure of 140 systolic, 70 diastolic, with a hemoglobin of 2.5 gm. per 100 cc. indicates that the heart must still have been reasonably normal in spite of some congestion of the lungs when she entered the hospital.

DR. ELLIS: I agree; I certainly believe that whatever heart disease she had was probably aggravated by the anemia.

DR. BENJAMIN CASTLEMAN: Dr. Point, have you any comment?

DR. WARREN POINT: I think the lesion was in the small bowel because of the nature of the discomfort.

DR. CASTLEMAN: Certainly, the fact that she had had this disease for at least three years is in favor of a benign lesion or one of low-grade malignancy. I think everybody agreed that it was almost certainly in the small bowel, since the x-ray findings were negative. The small bowel, as we know, is one of the places where the radiologist can easily miss a small lesion.

CLINICAL DIAGNOSIS

Small-bowel hemorrhage.

DR. DANIEL S. ELLIS'S DIAGNOSIS

Leiomyoma of small bowel.

ANATOMICAL DIAGNOSIS

Massive bleeding from carcinoid of terminal ileum, with metastases to regional lymph nodes.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: This patient would have been operated on much earlier if she had not repeatedly refused to submit to surgery before the last admission.

*Case Records of the Massachusetts General Hospital (Case 39331). *New Eng. J. Med.* **249**:287-293, 1953.

The surgeon operated with a diagnosis of small-bowel hemorrhage. At operation a lesion was located about 15 cm. from the ileocecal valve in the terminal ileum and was resected. The lesion was a tumor about 3 cm. in diameter that projected slightly into the lumen. The mucosa over it was granular and appeared to have been the source of bleeding. It extended into the muscularis of the small bowel, and on gross examination looked like an intramural tumor such as a leiomyoma or a neurofibroma. The resected specimen included a large section of the mesentery in which there were several nodules, one measuring 1 cm. in diameter. Microscopical examination showed that this lesion was not a connective-tissue tumor but a carcinoid or argentaffinoma. It is very unusual for small-bowel carcinoids to bleed; usually, they produce symptoms of obstruction caused by the adjacent metastatic lymph nodes. Four out of eight lymph nodes were positive for metastases of carcinoid. This is a low-grade malignant tumor. Perhaps less than 50 per cent in the small bowel metastasize; the ones in the appendix, where this tumor is most common, do not metastasize.

This patient's postoperative course was quite stormy; resection of another loop of bowel, whose blood supply had apparently been compromised at the first operation, was required, and, unfortunately, she died. Autopsy showed a large heart and a very large aneurysm of the heart wall from a healed myocardial infarct — evidence of old coronary-artery disease. The liver was slightly enlarged and at the time of autopsy was down 5 cm. below the costal margin. The lungs contained no tumor.

CASE 40182

Presentation of Case

First admission. A thirty-five-year-old woman was admitted to the hospital because of abdominal soreness.

The patient had had asthma since the age of three years, with exacerbations each spring. Eight years before entry, while she was pregnant, the asthma became worse; an x-ray film of the chest was said to show tuberculosis. She was sent to a sanatorium for three weeks but was discharged when all studies were negative. Three years before entry she had a "phlebitis" of the left leg that was treated by ligation of the inferior vena cava; the clot was found to have extended above the superficial femoral vein. Since then the patient had ankle swelling after long walks. In the few months before entry the asthma had been worse. Six weeks before admission she had a severe bout of asthma, with a temperature of 103°F., and was treated at another hospital with penicillin, oxygen and two blood transfusions. Soon afterward the abdomen began to swell and became painful; for a short while before admission the soreness, which was midepigastric and dull, became steady and severe enough to keep her awake. She noticed that in the evening the ankles were swollen. The asthma and dyspnea had not become worse. There had been some recent weight loss.

Physical examination revealed a thin, wasted, cyanotic woman with mild respiratory distress. Brown, flat lesions, 3 mm. in diameter, were scattered on the back and anterior portion of the chest. There was mild clubbing of the fingers and toes, and the nail beds were cyanotic. On the tongue were sharply demarcated lesions with central reddened areas, white borders and irregular outlines. The neck veins were distended in the upright position. The chest tended to be barrel shaped. Expiration was prolonged. There was dullness to percussion, and increased tactile and vocal fremitus in the lower right part of the chest. There were scattered inspiratory coarse crackles and many expiratory wheezes and musical sounds. The heart did not appear to be enlarged. A diastolic gallop was heard at the apex, and a Grade 2 systolic murmur was audible over the precordium, loudest at the apex. The pulmonic second sound was greater than the aortic. The abdomen was protuberant. The liver was enlarged to percussion, but the edge could not be felt. No abdominal fluid could be demonstrated. There was + + + sacral edema and + + edema of both legs up to the knees.

The temperature was 98.2°F., the pulse 136, and the respirations 32. The blood pressure was 120 systolic, 90 diastolic.

The urine had a specific gravity of 1.015 and gave a + + reaction for albumin. Examination of the blood revealed a hemoglobin of 17 gm. and a white-cell count of 12,800, with 86 per cent neutrophils. The nonprotein nitrogen was 18 gm., and the total protein 6.59 gm. per 100 cc., with a normal albumin-globulin ratio; the sodium was 134.3 milliequiv., the chloride 78 milliequiv., the potassium 6 milliequiv., and the carbon dioxide 41.7 milliequiv. per liter. The blood pH was 7.22. A tuberculin test was negative. Guinea pigs inoculated with sputum were negative for tuberculosis. An electrocardiogram showed right-axis deviation. A roentgenogram of the chest (Fig. 1) demonstrated all the visualized lung to contain emphysematous blebs and dilated bronchi. Each upper lobe was reduced in size, and there was fluid in each pleural space. There was considerable density surrounding the apex of each lung. The proximal portions of the pulmonary arteries and each lung root seemed enlarged. The right border of the superior mediastinum was displaced somewhat laterally. The bifurcation appeared widened. The heart appeared to be considerably enlarged, probably most prominently on the right side. Both leaves of the diaphragm were low, and motion was limited. The trachea and esophagus disclosed slight evidence of extrinsic pressure to the right in the lower part of the neck. X-ray

films of the abdomen showed the liver to be probably enlarged and low. A gray quality to the film suggested intra-abdominal fluid. A film of the hand revealed cystic changes in some of the carpal bones.

The patient was treated with digitalis, aminophylline, ephedrine, potassium iodide, sedatives and oxygen. A paracentesis on the fourth hospital day yielded 400 cc. of slightly cloudy fluid, with a specific gravity of 1.010, that contained 150 red cells and 8260 mononuclear white cells per cubic millimeter; no tumor cells were found. She remained cyanotic, dyspneic and in a seemingly terminal state. Administration of cortisone was begun on the fourth day. She gradually improved. Lung-function studies showed that the vital capacity was 400 cc. (predicted value, 3.1 liters) and the maximum breathing capacity 18 liters per minute (predicted level, 74 liters). The patient was discharged improved after a month in the hospital.

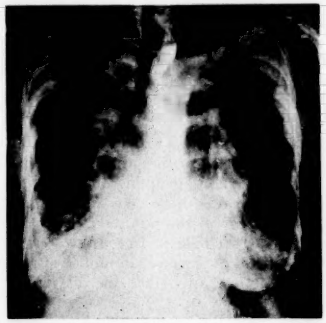

FIGURE 1.

Second admission (six weeks later). On limited activity she was able to live fairly comfortably until a few days before admission, when weakness and dyspnea became severe. Physical examination revealed no significant changes. She was treated with penicillin and cortisone, improved and was discharged after two weeks.

Final admission (two months later). She had continued on a diet moderately low in sodium, digitalis and aminophylline as needed. Temporarily she improved and felt much better. Two days before entry dyspnea and orthopnea became severe, and she had headache and pain in the right lumbar region.

Physical examination revealed an emaciated, cyanotic woman in great respiratory distress. The neck veins were distended. The chest was hyper-resonant. There were wheezes throughout, and crackling rales at both bases. The heart rate was irregular at a rate of 140. There was a Grade 3 apical systolic murmur. The pulmonic second sound was much greater than the aortic. The liver was questionably enlarged.

The temperature was 100°F., and the respirations 40. The blood pressure was 90 systolic, 70 diastolic.

The urine was normal. Examination of the blood showed a hemoglobin of 17 gm. and a white-cell count of 7300. The sodium was 130 milliequiv., the chloride 84 milliequiv., the carbon dioxide 40 milliequiv., and the potassium 6.4 milliequiv. per liter. An electrocardiogram demonstrated hypertrophy of the right ventricle and ST-segment and T-wave changes consistent with those resulting from digitalis or tachycardia. A later electrocardiogram disclosed atrial fibrillation.

The patient was maintained on the same medication and penicillin and later quinidine. She became cold and more cyanotic, and the blood pressure fell. She died suddenly on the second hospital day.

DIFFERENTIAL DIAGNOSIS

DR. LEWIS W. KANE*: In summary this thirty-five-year-old woman had a history of seasonal asthma since infancy. Until eight years previously (at the age of twenty-seven) there was no indication that she was about to enter a period of serious pulmonary and cardiac difficulties that would result in death. The first signs of serious pulmonary disease appeared after pregnancy, when a chest film resulted in her admission to a tuberculosis sanatorium for further study. Eight years later and six months before she died she had a severe bout of asthma, with a temperature of 103°F. That this was not uncomplicated asthma is attested by the high fever and the necessity for blood transfusions. From this point on the tempo of her illness quickened until her death six months later.

May we see the x-ray films?

DR. JOHN F. GIBBONS: The first available chest films taken during the first admission show gross abnormalities in both lungs in that all lobes appear to contain emphysematous blebs and dilated bronchi (Fig. 1). There is evidence of marked fibrosis bilaterally and diffuse thickening of the pleura, primarily over the upper lateral chest wall and apexes. The costophrenic angles are blunted, possibly owing to thickened pleura or fluid, which may also account for the apical thickening. The upper mediastinum is displaced moderately to the right, and there is apparent widening of the carina at the origin of the right main-stem bronchus. The right-ventricle portion of the heart is abnormally prominent, and there is increased diameter of the main pulmonary vessels.

Fluoroscopically, diaphragmatic motion was limited bilaterally and the leaves of the diaphragm were abnormally low.

In summary the changes suggest diffuse pulmonary emphysema and marked bilateral fibrosis of the lungs associated with bronchiectasis and cor pulmonale. Films of the abdomen made at the same time show the liver to be lower in position and moderately en-

*Assistant in medicine, Massachusetts General Hospital.

larged. There is evidence of ascites, which obscures visceral outlines. Films of the hands demonstrate cystic changes in the left navicular and capitate bones. The significance of these changes is not apparent.

During the next three months repeated films of the chest showed no significant changes as compared with the original films.

DR. KANE: When I first read this history I thought this might be a case of multiple silent pulmonary emboli, with subsequent cor pulmonale, such as those recently described by Owen et al.[1] That she had cor pulmonale in failure is amply supported by the enlargement of the right ventricle, the increased diameter of the main pulmonary vessels, the right-axis deviation observed on the electrocardiogram, the distended neck veins, the gallop rhythm, the ascites and the edema of the legs. The phlebitis to a level high enough to require ligation of the inferior vena cava provided a convenient source for embolization. However, the more I reviewed the history, the less convincing this diagnosis became. What deters me most from such a diagnosis is the striking pulmonary picture presented by this case. In the cases reported by Owen and his associates[1] there were no recognizable episodes suggesting repeated pulmonary emboli. The symptoms were attributable to cor pulmonale and cardiac failure. The chest films showed surprisingly little and were not of much help in diagnosis. In the case under discussion, in addition to the striking x-ray findings in the chest, there was ample evidence of ventilatory embarrassment as indicated by the low vital capacity and maximum breathing capacity as well as the elevated serum carbon dioxide.

Pulmonary fibrosis seems to me to have been the primary difficulty in this case with secondary emphysema, cor pulmonale and cardiac failure. Fibrosis may be the sequel to a number of varieties of injury to the lung. Unresolved pneumonia, healed infarcts, silicosis, berylliosis, lipoid pneumonia, scleroderma, polyarteritis nodosa, tuberculosis and sarcoidosis, as well as a host of other conditions, both known and unknown, all result in pulmonary fibrosis that may be very similar in appearance. Pulmonary fibrosis leads to decreased elasticity and diminished ventilatory capacity. The collapse and destruction of alveolar tissue produces a disproportion between thoracic and pulmonary volumes and hence emphysema and bronchiectasis. The decrease in vascular bed results in pulmonary hypertension, cor pulmonale and persistent right-sided heart failure.

In the absence of a definite supporting history, I shall have to eliminate lipoid pneumonia, silicosis and berylliosis as causes of the difficulty. Also, there is little to substantiate the diagnosis of scleroderma or polyarteritis nodosa. Tuberculosis has already been eliminated.

Organized pneumonia, which may be responsible for pulmonary fibrosis, is often found in persons with chronic bronchial asthma and may be the cause of death in these cases. The mechanism by which bronchial asthma delays the resolution of the pneumonic process and favors organization is unknown. Ten of the 59 cases of pulmonary fibrosis reported by Mallory[2] were due to organized pneumonia in patients with a history of chronic bronchial asthma.

This patient had had asthma since the age of three years. The bout of asthma with a temperature of 103°F. six weeks before entry sounds more like a pneumonic process than uncomplicated asthma. Perhaps some of the other "asthmatic" attacks were bouts of pneumonia hidden, distorted or disguised by antibiotics. If they were, it is possible that her difficulty was due to repeated bouts of pneumonia followed by organization. However, there seems to have been too much pleural reaction in this case for me to believe that organization of the usual variety of bacterial or viral pneumonia was responsible.

Interstitial pulmonary fibrosis of unknown etiology has been described by Hamman and Rich[3] and Fienberg[4] as well as others. Some of these cases may have resulted from organization of interstitial pneumonitis of bacterial or viral origin. Other cases appear to be more closely linked histologically to diffuse cholesterol pneumonitis.

Sarcoidosis is a tempting diagnosis. The skin lesions and cysts in the carpal bones as noted in the history make such a diagnosis tempting; however, on close examination the carpal-bone cysts are not impressive, and the description of the skin lesions is not characteristic of dermal sarcoidosis. In the absence of uveitis, parotitis, dactylitis, splenomegaly and lymphadenopathy I have little to strengthen the diagnosis of sarcoidosis as we usually see it. I add "as we see it" since sarcoidosis is usually a benign disease with a marked tendency to regress within two years.

The late Tracy B. Mallory described a condition that he termed granulomatous pneumonitis.[2] In these cases symptoms appeared in the thirties, and the disease progressed relentlessly to death in three to ten years. The outstanding symptom was dyspnea, and in 4 of the 6 cases described cor pulmonale was present. The degree of pulmonary fibrosis was extensive in all cases. On gross examination the pleura was thick and distorted and deeply pitted by scars alternating with emphysematous bullae. In some cases the lungs were multilobular, with an appearance like that of a cirrhotic liver. Histologically, there were tubercle-like collections of epithelioid and giant cells surrounded by fibroblasts. These developed in the interstitial tissue—never in the lumens of the alveoli or air passages. The oldest lesions were found in the alveolar walls. Contiguous lesions eventually fused, invading and destroying bronchi and blood vessels. Foci of necrosis developed, but never caseation. The etiology of granulomatous pneumonitis is obscure. Mallory considered that it might be a localized sarcoidosis since in only 2 of the 6 cases were lesions found in organs other than the lungs.

I know of no certain way to differentiate the various types of idiopathic pulmonary fibrosis. Although this case seems to fit easily into the group of granulomatous pneumonitis, I should not be surprised if it turned out to have been idiopathic interstitial pulmonary fibrosis as described by Hamman and Rich.[3]

In summary my diagnoses are pulmonary fibrosis and secondary emphysema, caused by granulomatous pneumonitis or organized pneumonitis of unknown etiology, cor pulmonale and right-sided heart failure.

DR. FARAHE MALOOF: Dr. Kane has given an excellent discussion of the differential diagnosis; our thoughts were similar concerning the underlying pulmonary disease. I saw this patient only during the second admission. Two important questions arose concerning therapy. In the first place, did cortisone really turn the tide during the first admission, and should it have been continued? I was not convinced of its presumed initial benefit in view of the apparent nature of the underlying pulmonary disease and the simultaneous use of numerous other therapeutic measures; therefore, I suggested that we gradually stop the cortisone, which had been reinstituted, since a pulmonary infection seemed to have precipitated the most recent trouble. Secondly, should chronic antibiotic treatment have been given in an attempt to prevent further infection? Dr. Thomas F. Paine believed that such a program should be instituted and suggested that sulfamerazine, 0.5 gm., be given by mouth every twelve hours.

Several other interesting points should be mentioned: the aggravation of the asthma by the pregnant state, which usually ameliorates certain diseases that respond to steroids; the amenorrhea, which was probably secondary in part to the debilitating disease; the intermittent use of ammonium chloride, which did not aggravate the respiratory acidosis; and the hyponatremia, which may have been caused by several factors but has been noted in some patients with severe pulmonary disease, usually tuberculosis, and is not related to adrenal insufficiency.

CLINICAL DIAGNOSES

Cor pulmonale.
Chronic pulmonary fibrosis.
Chronic pneumonitis.

DR. LEWIS W. KANE'S DIAGNOSES

Pulmonary fibrosis due to granulomatous or organized interstitial pneumonitis, with secondary emphysema.
Cor pulmonale and right-sided heart failure.

ANATOMICAL DIAGNOSES

Pulmonary fibrosis, severe, generalized.
(Bronchial asthma, with superimposed pneumonitis.)
Cor pulmonale.

PATHOLOGICAL DISCUSSION

DR. WINFIELD S. MORGAN: I think it is fair to say that a case of this type frequently poses as difficult a problem for the pathologist as it does for the clinician from the standpoint of diagnosis. For when the end stage of a pathologic process is fibrosis, and that stage is the only one available for study, one may find it hard to determine with any degree of certainty the nature of the lesion that led to the fibrosis.

Aside from the ligature about the inferior vena cava abnormal findings at autopsy were confined to the chest, where the pleural cavities were completely obliterated by fibrous adhesions of such density that the lungs could only be removed by sharp dissection. In many places the pleura measured up to 1 cm. in thickness. The bronchial lymph nodes were moderately enlarged and were reactive in appearance. The pericardium was normal. The heart weighed 360 gm., and although we would ordinarily consider this to be within normal limits, I think we must assume that it was somewhat enlarged in view of the fact that the patient weighed only 75 pounds. The heart was normal except for a well developed cor pulmonale in which the right ventricle was 7 mm. thick, the normal measurement being 3 or 4 mm. Although evidence of pulmonary hypertension was slight on gross examination of the larger branches of the pulmonary artery there was marked intimal proliferation with luminal narrowing of the secondary and tertiary radicles that could be better appreciated microscopically.

The lungs weighed 1250 gm. and were not large and billowy as in many patients with bronchial asthma but were firm and rather contracted. On section they presented a striking appearance characterized by diffuse, severe fibrosis, which involved every segment. Fibrosis seemed to be more severe at the level of the hilus and beneath the pleura, with fibrous bands and patches of varying size and shape ramifying in all directions separating the lung parenchyma into small irregular islands and giving it a honeycomb appearance. The largest area of aerated parenchyma in either lung measured 4 cm. in diameter, and most were much smaller. They showed varying degrees of congestion or edema.

On microscopical examination there was little question that this woman had had bronchial asthma. The bronchi showed all the usual changes, including pseudostratification of the epithelium, marked thickening and hyalinization of the basement membrane, hypertrophy of the muscle and bronchial glands and a chronic inflammatory infiltration. The bronchial lumens contained only small amounts of mucus so that the immediate cause of death was not status asthmaticus. The fibrosis observed grossly usually took the form of roughly stellate, often connecting patches consisting of dense collagenous connective tissue scattered throughout which might be occasional bronchioles or alveoli. Although on routine stains these

fibrous patches appeared to be composed only of dense collagenous scar tissue elastic-tissue stains revealed that often the alveolar pattern could still be discerned (Fig. 2). Elsewhere, in less involved areas,

FIGURE 2.

some of the alveoli contained similar organized and hyalinized plugs presumably representing past organization of intra-alveolar exudate. Although a few of the alveolar walls showed some thickening this was not general, and there was little evidence that the process leading to the fibrosis was one of interstitial pneumonitis. Almost all the remaining pulmonary parenchyma demonstrated moderate to severe emphysema.

I believe Dr. Kane has covered most of the possible causes of the fibrotic changes in the lungs. We can rule out multiple silent pulmonary emboli since elastic-tissue stains did not reveal condensation of alveolar elastic fibrils as seen in healed pulmonary infarcts. Sarcoidosis, tuberculosis and other granulomatous processes are ruled out by the absence of lesions suggestive of these diseases in multiple sections from each segment. There was no evidence of any of the so-called collagen diseases or of lipoid pneumonia. Although, clinically, the diffuseness of the pulmonary lesion, the cor pulmonale and the chronic pulmonary insufficiency should bring to mind the possibility of an interstitial type of fibrosis such as that described by Hamman and Rich[3] the histologic findings just described rule out this disease in the case under discussion. There is little question that the distribution of the fibrosis, the preservation of the alveolar outlines within the fibrous patches, as demonstrated by elastic-tissue stains, and the isolated alveoli containing organized exudate indicate that the antecedent process leading to the pulmonary fibrosis was one of recurrent bouts of organizing pneumonitis occurring over many years with gradually diminishing pulmonary reserve. In this condition, fibrous tissue may develop in large amounts within the smaller air passages and the alveoli as a result of organization of fibrin produced in the course of bronchitis or pneumonic exudation that has failed to undergo resolution. As Dr. Kane pointed out, the mechanism by which bronchial asthma delays the resolution of the pneumonic process and favors organization is not clear.

Although we are all more impressed by the asthmatic patient who dies in an acute attack from plugging of the bronchi with mucus, severe pulmonary fibrosis with chronic insufficiency may represent a no less serious complication. Dr. Kane has referred to Mallory's[2] study of 59 patients with pulmonary fibrosis, in 19 of whom this was of the organized, pneumonic type; 10 were patients with bronchial asthma, and in 6 of these the fibrosis was clinically significant. One wonders what effect the present use of cortisone in the treatment of asthma will have on patients subject to recurrent pneumonitis and whether in the years to come we shall see more or fewer asthmatic patients who die of pulmonary fibrosis.

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FIRE, SMOKE AND WATER

THE Chemical Laboratory of the American Medical Association, in a series of ingenious and carefully controlled experiments,[1] demonstrated last year that a certain type of cigarette filter was apparently capable of effecting a reduction of 41 to 60 per cent of the nicotine and of 44 to 55 per cent of the tars in the main smoke stream from cigarettes.

A firm of cigarette manufacturers, in a recent full-page newspaper advertisement, called attention to these tests, which had already been publicized in the daily press, with the statement that the type of filter demonstrated by the American Medical Association as being the most effective of those tested for these purposes was attached only to cigarettes manufactured by this firm. The American Medical Association,[2] responding editorially with what seems to have been hair-trigger alacrity, accuses the advertiser of "unauthorized and medically unethical use of the prestige and reputation of the American Medical Association and THE JOURNAL" in a manner that "constitutes an outrageous example of commercial exploitation of the American medical profession" and provides, by its blatant implication, "a most reprehensible instance of hucksterism." The editorial, however, does not deny the advertiser's claim.

The language and the accusations seem somehow intemperate, and many of its most loyal members must unhappily wish that their association did not at times react so violently to the stimuli that the world about it is so certain to provide. *The New England Journal of Medicine* holds a brief for no cigarette and no advertiser, but it has a degree of cautious receptiveness for any promising effort to control any irritating factor that seems to be associated with the smoking of cigarettes. There appears to be some hope that the filter in question may aid in this control and may be a step in the direction of removing a possible carcinogenic factor from cigarette smoke although not so stated by the advertiser. Whereas the main efforts of the Tobacco Industry Research Committee[3] seem directed toward a refutation of the implication that cigarette smoke contains carcinogenic factors at all, the employment of an even partly effective filter by this company suggests a tacit acknowledgment of the possibility and willingness to do something about it.

One may question whether the writer of the American Medical Association's outspoken rebuttal[2] could have read with care the advertisement in question, which contains nothing to rebut unless it should develop that the type of filter found most effective in removing tars and nicotine was not, at the time of the advertisement, used exclusively by the advertiser. As stated above, this claim was not denied.

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WORLD FEDERALISM

PHYSICIANS are generally regarded as educated leaders of society, many of whom take part in civic affairs and contribute to the general welfare of the community. Many others, however, seem to be interested only in their own activities and their practices. It is time for them to realize that times have changed, that minority groups are constantly getting together and making themselves heard on matters that may

adversely affect the American way of life, and that thoughtful citizens of every status must make their own voices heard. Whereas fifty years ago world problems were of relatively minor importance to the average person, comfortably separated by two oceans from potential enemies, it is now apparent that oceans are no protection and that world war may yet supervene unless more active efforts are made to substitute world peace for it. It is comparatively easy to stir up enthusiasm to protect one's own country and one's allies in case of war, but it is not so easy to get people to work actively for peace.

The future of the world in general and of this country in particular and of each person as an individual depends on world peace, and yet the only major world organization that is working for peace is the United Nations. Therefore, the United Nations must be supported in every way possible. Peace, freedom and security are regarded as three of the fundamentals in the American way of life, but is the country at peace and is it free? Hardly, so long as a truculent power can force it to spend over 60 per cent of the national income on armaments. Are the American people secure? No, for the federal Government can no longer provide complete security. Since no religious belief or political philosophy that the world has ever known has been able to divert a single nation from a path of war, should not some sort of world federal government have at least the opportunity of trying to give all people the protection against war that is no longer within the power of national governments? To this end the United World Federalists, Incorporated, has issued a "call for the support and strengthening of the United Nations and for such amendments to its Charter as will enable it to achieve universal disarmament enforced under adequate safeguards, thus preventing aggression and making possible a world at peace under law."

At first thought this may seem visionary, but in 1955 there will probably be a review of the United Nations Charter with a view to its amendment. It is possible that at this time veto power will be taken away so far as questions involving pacific settlement of disputes and admission of new members with stable governments inclined to co-operate are concerned. Such a step might lead by weight of world opinion to universal disarmament under adequate safeguards.

COURSES IN MEDICAL JOURNALISM

Some months ago a peripatetic correspondent of the London *Lancet* proposed, in lighter vein, a royal college of medical scribes. Under the guidance of such an academic establishment the lives of those intended for the monastic vocation of medical writing would truly be dedicated to their career. Starting at the age of twelve, they would begin their preliminary studies with Greek, to be followed by Latin, English, the medical sciences, medical history and a complete, if abbreviated, medical curriculum, preparatory to the more formal training in their art.

Little did the *Lancet's* correspondent know how soon a modified concept of this dream might be realized. As a result largely of the efforts of the Educational Committee of the American Medical Writers' Association, four-year courses in medical journalism are about to be inaugurated and will in fact be prepared to accept students next September at the School of Journalism and Communications of the University of Illinois and the School of Journalism of the University of Missouri. In the latter school, which, it is said, is the oldest in the world devoted to journalism, having been established in 1908, the medical program is being worked out in co-operation with the university's new four-year school of medicine.

In both institutions the program has been devised with the aid of the American Medical Writers' Association. According to this plan a fourth of the student's time will be devoted to courses in professional journalism and three fourths to academic courses, including basic and medical sciences. To further the project the Association has started a medical-journalism scholarship fund.

With over 10,000 periodicals in current publication, medical journalism is probably the most prolific source of so-called nonfictional literature in the world, aside from the reporting of current events. And yet no formal courses of training leading to a degree in this specialized field of literature have ever been offered, according to the announcements.

The most important consideration in such a venture concerns the practical purposes to which such an education can be put, for most excursions into higher learning must have their economic as well as their cultural goals to achieve. Physicians, who still do most of the medical writing, can hardly be expected to undergo a special training for this purpose; many of them can, however, be educated to appreciate their lack of training and to admit the necessity for writer assistants to edit that which they have put on paper. Thus, there exists a limited field for independent editing, which probably can be extended.

It is with medical journals and medical publishers, however, that personnel trained in medical writing should find its most constant employment. Further uses for such a training should be with clinics, hospitals and pharmaceutical houses, and it is not too much to hope that eventually a new breed of trained, scientific, discerning and conscientious medical and scientific reporters may be developed, conscious of their obligations to both the profession they are interpreting and the public they are trying to serve. Then will a millennium have been reached indeed.

WHO EXECUTIVE BOARD REPORTS

THE program for 1955 of the World Health Organization, as released by its Executive Board in February, calls for a budget of $10,300,000. The "well-conceived" program of the director-general, as it is termed by the Executive Board, is planned to finance health activities in 117 countries and territories and will suffer materially if the full sum requested is not forthcoming. The proposed budget is $1,800,000, or 21 per cent over that of 1954. The largest single item in this increase is more than $600,000 for personnel to continue joint UNICEF (United Nations International Children's Emergency Fund) and WHO projects for child-health programs.

In relation to program developments it is noted that WHO activities will register a shift from attacks on specific communicable diseases to an increased accent on the positive promotion of health. Occupational health in particular, especially in newly industrialized countries, will be stressed if the Assembly heeds the advice of its executive board. To this end further co-operation between the International Labour Office and WHO will be essential.

Further studies recommended include one concerning international regulations for the protection of workers and the public against roentgen and isotopic radiations, suggested by the government of Austria, and one on the standardization of laboratory tests for foods. It was decided that this should be limited for the moment to "intentional chemical additives."

Eighty items in all were considered at the meeting, among them being a request on behalf of the League of Arab States "for the establishment of a form of understanding and co-operation with WHO"; such relations have already been initiated. Official relations were also established with three nongovernmental agencies — the International Committee of Catholic Nurses and Medico-Social Workers, the Medical Women's International Association and the Union O. S. E. (Union of Sanitary Engineers?). Darling Foundation prizes were awarded to Dr. G. Robert Coatney, Bethesda, Maryland, and Professor George Macdonald, of London, for their work on malaria control; and on behalf of the Health Assembly the Board accepted gifts of $3500 from the Government of Brunei and $20 from the Saturday Club of Washington, D. C.

The Emperor Napoleon has just established a system in Paris, whereby the poor can receive gratuitous medical attendance at their own houses.

Boston M. & S. J., *May 10, 1854*

MASSACHUSETTS MEDICAL SOCIETY

STATED MEETING OF THE COUNCIL

A stated meeting of the Council will be held in the Georgian Room, Hotel Statler, Boston, on Monday, May 17, at 7 p.m.

Business:

1. Call to order at 7 p.m.
2. Presentation of record of meeting held February 3, 1954, as published in Vol. 250, Supplement No. 1, March 11, 1954, of the *New England Journal of Medicine.*
3. Reports of standing and special committees.
4. Such other business as may legally come before this meeting.

ROBERT W. BUCK, M.D.
Secretary

DINNER FOR PRESIDENTS OF DISTRICT MEDICAL SOCIETIES

The annual dinner for the presidents of the district medical societies of the Massachusetts Medical Society will be held in Parlor C of the Hotel Statler, Boston, on Tuesday, May 18, at 6:30 p.m.

The president-elect of the Society has invited the presidents of the district societies, who, by reason of their office, are not only vice-presidents of the Massachusetts Medical Society, succeeding in order of seniority of membership, but also members of the Council, to attend the annual dinner for the presidents of the district societies and to discuss their duties and responsibilities.

SECTION OF INDUSTRIAL HEALTH

During the past several years many members of the Society have told me that during the course of the annual meeting they would have attended the annual luncheon of the Section of Industrial Health "if they had been members of the Section." It is called to the attention of the members that anyone interested in any particular subject, whether it is industrial health or medicine or any other, automatically becomes a member of that section, and is thereby welcome to attend its annual luncheon.

As chairman of the Section of Industrial Health, I invite all interested members to attend a luncheon of the Section of Industrial Health at noon on Wednesday, May 19, 1954, at the Hotel Statler in Boston. A dynamic speaker, Dr. Robert Collier Page, president of the Industrial Medical Association, will address us on the subject "Industry's Contribution to the Future of Medicine."

GEORGE E. MORRIS, M.D.
Chairman

NOTICES

WILINSKY LECTURE

The Wilinsky Lecture will be delivered by Dr. Charles F. Wilinsky in the Jimmy Fund Building Auditorium on Friday, May 14, at 4:30 p.m., instead of as previously announced.

NEW ENGLAND PEDIATRIC SOCIETY

A meeting of the New England Pediatric Society will be held in Providence, on May 12. The program is as follows:

12 m. Clinicopathological conference. Peters House Auditorium, Rhode Island Hospital, 595 Eddy Street, Providence, Rhode Island.

1 p.m. Lunch. Rhode Island Hospital.

2 p.m. Scientific session. Dr. Robert M. Lord, presiding. Peters House Auditorium, Rhode Island Hospital.

5-6 p.m. Refreshments and dinner. Agawam Hunt Club, East Providence, Rhode Island. (Dinner, $3.75.)

7 p.m. Some Virtues and Vices of Metabolism. Dr. Victor A. Najjar, Johns Hopkins Hospital, Baltimore, Maryland.

SIGMA XI LECTURE

The Sigma Xi Lecture will be delivered by Dr. Harry C. Solomon, professor of psychiatry, Harvard Medical School, in the Allston Burr Lecture Hall, Harvard University, Broadway and Quincy streets, Cambridge, on May 25 at 8 p.m. The topic will be "Psychiatry, Its Scope and Its Research Potentials." Physicians and students are invited.

SOCIETY MEETINGS AND CONFERENCES

May 6–26. Consultation Clinics for Crippled Children. Page 705, issue of April 22.

May 10. New England Cardiovascular Society. Henry Jackson Lecture. Page 708, issue of April 22.

May 10–12. Institute of Industrial Health. Page 491, issue of March 18.

May 11. Harvard Medical Society. Page 707, issue of April 22.

May 12. Middlesex East District Medical Society. Annual Meeting. (Harlow Dinner.)

May 12. Essex North District Medical Society Meeting. Andover Country Club, Andover.

May 12. New England Obstetrical and Gynecological Society. Spring Meeting. Longmeadow Country Club, Springfield.

May 12. New England Pediatric Society. Notice above.

May 14. Wilinsky Lecture. Notice above.

May 14–16. Fifth Annual International Group of Doctors in Alcoholics Anonymous. Page 1004, issue of December 10.

May 14–16. American Academy of Dental Medicine. Page 38, issue of January 7.

May 15. Massachusetts Hospital School. Orthopedic Rounds. Page 165, issue of February 11.

May 17–21. Examination, American Board of Otolaryngology. Hotel Statler and Massachusetts Eye and Ear Infirmary.

May 17–23. National Tuberculosis Association. Page 663, issue of April 15.

May 18–20. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston. Page 740.

May 19. Massachusetts Medical Society. Section of Industrial Health. Page 791.

May 21. Boston Lying-in Hospital Journal Club. Page 38, issue of January 7.

May 25. Sigma Xi Lecture. Notice above.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, MAY 13

THURSDAY, MAY 13

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

*9:00–10:00 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

11:00 a.m. Staff Conference. Recent Knowledge of the Rh Factor in Medical Practice. Dr. Fred H. Allen, Jr. Regional Office of the Veterans Administration, Conference Room, 4th floor, 17 Court Street, Boston.

*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

11:00 a.m. Thoracic Conference. The Embryological Background of Congenital Defects of the Heart (Moving Pictures). Drs. Dwight E. Harken and Harrison Black and the Thoracic Service. Main Amphitheater, Peter Bent Brigham Hospital.

*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

5:00 p.m. Case Presentation and Pathological Discussion. Followed by a Subject of Special Presentation. Joslin Amphitheater, New England Deaconess Hospital.

8:30 p.m. Pentucket Association of Physicians. Practical Consideration in Treatment of Poliomyelitis. Dr. David S. Grice. Haverhill Country Club. Gile Street, Haverhill.

FRIDAY, MAY 14

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

12:00 m.–1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.

*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.

*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

*4:30 p.m. Wilinsky Lecture. The Relation of Hospitals and Health Departments in Tomorrow's World. Dr. Charles F. Wilinsky. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.

SATURDAY, MAY 15

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.

*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–12:00 m. Hematology Clinic. Dr. William Dameshek. Pratt Auditorium, New England Center Hospital.

*11:00 a.m.–12:00 m. Intermediary Metabolism. Dr. G. H. Stueck. Veterans Administration Hospital, Room 132, White River Junction, Vermont.

MONDAY, MAY 17

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Foot Problems. New England Deaconess Hospital.

*8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

12:00 m. Pediatric Medical–Surgical Conference (Boston Floating Hospital). Pratt Lecture Hall. Joseph H. Pratt Diagnostic Hospital.

*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

7:00–9:00 p.m. Combined Anesthesia Resident Training Program. Jimmy Fund Building. Children's Medical Center, 35 Binney Street.

TUESDAY, MAY 18

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*12:00 m. Pediatric Grand Rounds. Cheever Amphitheater, Dowling Building. Boston City Hospital.

*12:00 m.–1:00 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.

*12:30–1:30 p.m. Medical Journal Club. Cafeteria, New England Deaconess Hospital.

*4:00–5:30 p.m. Anesthesia Teaching Conference. Dr. Etsten. Stearns Auditorium, New England Center Hospital.

*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.

*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.

WEDNESDAY, MAY 19

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.

*12:00 m.–1:00 p.m. Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.

*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.

12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.

*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.

*4:00–5:30 p.m. Fracture Lecture, Boston City Hospital.

*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.

*5:00–6:00 p.m. Cancer Society Telecast. Hormonal and Chemical Treatment of Cancer. Dr. Rulon W. Rawson. Children's Cancer Research Center, 35 Binney Street.

*Open to the medical profession.